



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ : A61K 31/56, 31/65, 31/66 A61K 31/70	A1	(11) International Publication Number: WO 86/ 00227 (43) International Publication Date: 16 January 1986 (16.01.86)
(21) International Application Number: PCT/US85/01202 (22) International Filing Date: 24 June 1985 (24.06.85) (31) Priority Application Number: 623,510 (32) Priority Date: 22 June 1984 (22.06.84) (33) Priority Country: US (71)(72) Applicant and Inventor: VEECH, Richard, L. [US/US]; 712 Brent Road, Rockville, MD 20850 (US). (74) Agent: KLOOSTER, John, W.; Hill, Van Santen, Steadman & Simpson, 70th Floor - Sears Tower, Chicago, IL 60606 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European		patent), GB (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent). Published <i>With international search report.</i>
(54) Title: ELECTROLYTE SOLUTIONS AND <i>IN VIVO</i> USE THEREOF (57) Abstract Electrolyte solutions which are useful in electrolyte and fluid therapy, parenteral nutrition, and dialysis. The Na:Cl ratio is normalized, plasma and cellular pH are normalized, and cellular co-factor ratios are normalized, in a manner which decreases toxicity over prior art solutions. The solutions employ at least one of the following near-equilibrium couples: (a) bicarbonate/CO ₂ ; (b) l-lactate/pyruvate; and (c) d-betahydroxybutyrate/acetoacetate.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GA	Gabon	MR	Mauritania
AU	Australia	GB	United Kingdom	MW	Malawi
BB	Barbados	HU	Hungary	NL	Netherlands
BE	Belgium	IT	Italy	NO	Norway
BG	Bulgaria	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali		
FR	France				

1 ELECTROLYTE SOLUTIONS AND IN VIVO USE THEREOF
DESCRIPTION

This invention lies in the field of in vivo techniques and compositions for replenishing fluid electrolytes and nutrients while regulating metabolic processes in living mammals.

State of the Art

The vital functions of highly developed organisms are closely dependent on the internal aqueous medium and on the maintenance in it of extreme constance of chemical and physical properties.

It has long been recognized that all animal intracellular and extracellular body fluids contain inorganic electrolytes, and that these electrolytes are involved in, and profoundly influence, various life processes. Attempts to make artificial electrolyte fluids which may bathe tissues or be administered to the human blood stream have been known since about 1880, and, although modern analytical tools and procedures have clarified compositional details of blood electrolytes, the use of various aqueous electrolyte solutions for in vivo purposes in human medicine and related fields has been extant for approximately one hundred years.

Those inorganic electrolytes characteristically found in normal human blood serum at respective concentration levels above about 1 millimolar per liter of concentration are shown below in Table I. Also, for comparative purposes, in Table I are shown some representative compositions of various aqueous electrolyte solutions that have been previously prepared and used for in vivo purposes. In general, the philosophy behind the formulation of aqueous electrolyte solutions for in vivo use has been that such should mimic or closely resemble the chemical composition of electrolytes in blood and plasma. An electrolyte is a sub-

1 stance (usually a salt, acid or base) which in solution
dissociates wholly or partly into electrically charged
particles known as ions (the term is also sometimes used
in the art to denote the solution itself, which has a
5 high electrical conductivity than the pure solvent,
e.g. water). The positively charged ions are termed
cations while the negatively charged ions are termed
anions. Strong and weak electrolytes are recognized.
The dissociation of electrolytes is very markedly depend-
10 ent on concentration: it increases with increasing
dilution of the solution. The ions can be regarded as
molecules in electrolyte solutions. Because of dis-
sociation considerations, the term "sigma" or the greek
letter for sigma ("Σ ") is sometimes employed herein
15 as a prefix to designate the total presence of a speci-
fied material, such as an electrolyte, whether or not
all of the material is in an ionic form complexed with
a heavy metal, or regardless of charge on the material
in a given solution. A pair of brackets ([]) indicates
20 the free concentration of the substance indicated as
opposed to that bound to tissue components, such as
proteins.

25

30

35=

Table I - Prior Art. Class Ia Solutions Containing 1 or 2 Cations, no Nutrients and No $\text{HCO}_3^-/\text{CO}_2$

Units	Normal Plasma	1. a. 1 Normal	1. a. 2 Normal	1. a. 3. Isotonic
moles	<i>N.E.J.M.</i>	0.9% Saline	0.95% Saline	Na Lactate,
-----	283, 1285	U.S.	U.K.	Salt
L fluid	1970			
Na	136 - 145	155	162.5	160.3
K	3.5 - 5.0			
Ca free [Ca ²⁺]	2.1 - 2.6 [1.06]			
Mg free [Mg ²⁺]	0.75 - 1.25 [0.53]			
mEq Cations	142.7-153.2	155	162.5	160.3
Cl	100 - 106	155	162.5	160.3
HCO_3	26 - 28			
Σ Pi	1 - 1.45			
SO_4	0.32 - 0.94			
L - lactate	0.6 - 1.8			52.0 (d,l)
pyruvate				
Lact/pyr				oo
D B OHbutyrate				
acetoacetate				
B HB/ acac				
acetate				
Other				
Σ mEq anions	128.7-139.4	155	162.5	160.3
Na/Cl	1.28 - 1.45	1.00	1.00	1.48
Glucose or others	3.9 - 5.6			
CO_2	0.99 - 1.39			
pH	7.35 - 7.45	5.5 - 6.5	5.5 - 6.5	~6.5
Σ mOsm	285 - 295	310	325	321

Use:

1. a. 1. Most common U.S. I.V. electrolyte solution, *Merck Manual*. Causes hyperchloremic acidosis with Na/Cl = 1.00. See Black DAK. *Lancet* i, 353, 1952.

1. a. 2. Used as "normal" saline in U.K. and Canada. *Geigy Handbook*.

1. a. 3. Darrow et al. *J. Am. Med. Ass.* 143: 365, 432, 1944. Normal Na/Cl ratio but causes abnormalities.

Table I (Cont'd) - Prior Art, Class 1b. Solutions Containing 1 or 2 Cations, HCO_3^- , and No Nutrients.

Units	Normal	1. b. 1.
mmoles	Plasma	Isotonic
-----	<i>W.E.J.N.</i>	NaHCO_3^- ,
L fluid	283, 1285	Salt
	1970	
Na	136 - 145	160.3
K	3.5 - 5.0	
Ca	2.1 - 2.6	
free $[\text{Ca}^{2+}]$	[1.06]	
Mg	0.75 - 1.25	
free $[\text{Mg}^{2+}]$	[0.53]	
$\Sigma \text{mEq Cations}$	142.7-153.2	160.3
Cl	100 - 106	108.3
HCO_3^-	26 - 28	52
ΣPi	1 - 1.45	
SO_4	0.32 - 0.94	
L - lactate	0.6 - 1.8	
pyruvate		
Lact/pyr		
D & DHbutyrate		
acetoacetate		
B HB/ acac		
acetate		
Other		
$\Sigma \text{mEq anions}$	128.7-139.4	160.3
Na/Cl	1.28 - 1.45	1.48
Glucose	3.9 - 5.6	
or others		
CO_2	0.99 - 1.39	
pH	7.35 - 7.45	8.6
ΣmOsm	285 - 295	321

Use:

1. b. 1. Darrow et al. *J. Am. Med. Ass.* 143: 365, 432, 1944. Use of Bicarbonate alone to correct Na/Cl ratio gives a solution with an abnormal pH, and one which will cause Ca^{2+} or Mg^{2+} added to the solution to precipitate as MgCO_3 or CaCO_3 . Is the common alternative to Na lactate, salt; 1. a. 3.

Table I (Cont'd) - Prior Art, Class 1c Solutions Containing 1 or 2 Cations, with Non-ionic Nutrients.
Typically 2.5%, 5%, 10%, 20% Glucose or Fructose in the U.S. and 2.52%, 5.25%, 10.5%, 20% Glucose or Fructose in the U.K.

Units	Normal Plasma	1. c. 1. 5% N.E.J.M. Dextrose in H ₂ O, U.S.	1. c. 2. 5.25% Dextrose in H ₂ O, U.K.	1. c. 3. Isotonic Glucose 2 + NaCl 1	1. c. 4. Glucose + NaLactate + NaCl	1. c. 10. D - S - W + 0.9% NaCl	1. c. 11. 10% Glucose + 0.9% NaCl	1. c. 12. 2.5% Glucose 0.45% NaCl	1. c. 13 5% Fructose in Electro- lyte 75
mOsm	283, 1285								
L fluid	1970								
Na	136 - 145			54.1	53.4	154	154	77	40
K	3.5 - 5.0								35
Ca free [Ca ²⁺]	2.1 - 2.6 [1.06]								
Mg free [Mg ²⁺]	0.75 - 1.25 [0.53]								
Σ mEq Cations	142.7-153.2	0	0	54.1	53.4	154	154	77	75
Cl	100 - 106			54.1	36.1	154	154	77	47.5
HCO ₃	26 - 28								
Σ Pi	1 - 1.45								7.5H ₂ PO ₄ ⁻
SO ₄	0.32 - 0.94								
L - lactate	0.6 - 1.8				17.3 (d,1)				20 (d,1)
pyruvate									
Lact/pyr					00				00
D B OHbutyrate									
acetoacetate									
B HB/ acac									
acetate									
Other									
Σ mEq anions	128.7-139.4	0	0	54.1	53.4	154	154	77	75
Na/Cl	1.28 - 1.45			1.00	1.48	1.00	1.00	1.00	0.34
Glucose or others	3.9 - 5.6	278	292	195	195	278	556	139	278 (Fructose)
CO ₂	0.99 - 1.39								
pH	7.35 - 7.45	~6.5	~6.5	~6.5	~6.5	~5.5 - 6.5	~5.5 - 6.5	~5.5 - 6.5	
Σ mOsm	285 - 295	278	292	301	302	561	813	293	428

Use:

1. c. 1. Most used I.V. solution in the U.S. *Merck Handbook*, 1966, p.1867. This is combined with NaCl in varying proportions so long as the osmolarity is not below 270 mOsm.
1. c. 2. Same solution in the U.K., where "isotonic" differs. *Geigy Handbook*, 1970, p. 334.
1. c. 3. *Geigy Handbook*, 1970, p. 334, has Na/Cl = 1.00
1. c. 4. *Geigy Handbook*, 1970, p. 334, has reasonable Na/Cl ratio but induces an abnormal redox state.
1. c. 10. through 1. c. 12. See *Facts and Comparisons* p. 51, Oct '81, Lippincott
1. c. 13. *Facts and Comparisons* p.52b Aug '83, Lippincott. Used in parenteral nutrition.

Table I (Cont'd) - Prior Art, Class 1d Solutions Containing 1 or 2 Cations, Nutrients, and $\text{HCO}_3^-/\text{CO}_2$.
None in prior art.

Units	Normal Plasma
moles	M.E.J.M.
-----	283, 1285
L fluid	1970
Na	136 - 145
K	3.5 - 5.0
Ca	2.1 - 2.6
free [Ca ²⁺]	[1.06]
Mg	0.75 - 1.25
free [Mg ²⁺]	[0.53]
Σ mEq Cations	142.7-153.2
Cl	100 - 106
HCO_3^-	26 - 28
Σ Pi	1 - 1.45
SO_4	0.32 - 0.94
L - lactate	0.6 - 1.8
pyruvate	
Lact/pyr	
D-B OHbutyrate	
acetoacetate	
B HB/ acac	
acetate	
Other	
Σ mEq anions	128.7-139.4
Na/Cl	1.28 - 1.45
Glucose	3.9 - 5.6
or others	
CO_2	0.99 - 1.39
pH	7.35 - 7.45
Σ mOsm	285 - 295
Use	

2f

Table I - Prior Art, Class 2a (Cont'd).

Units	Normal Plasma N.E.J.M. ----- 283, 1285 L fluid 1970	2. a. 13. Isolyte E (McGaw)	2. a. 14. Delbecco's Phosphate Saline	2. a. 15. Kreb's Ringer Phosphate
Na	136 - 145	140	152.2	150.76
K	3.5 - 5.0	10	4.17	5.92
Ca free [Ca ²⁺]	2.1 - 2.6 [1.06]	2.5	0.9	2.54
Mg free [Mg ²⁺]	0.75 - 1.25 [0.53]	1.5	0.49	1.18
Σ aEq Cations	142.7-153.2	158	159.15	164.12
Cl	100 - 106	103	140	131.51
HCO ₃	26 - 28			
Σ Pi	1 - 1.45		9.83	17.38
SO ₄	0.32 - 0.94		0.48	2.36
L - lactate	0.6 - 1.8			
pyruvate				
Lact/pyr				
D B OHbutyrate				
acetoacetate				
B HB/ acac				
acetate		49		
Other		4 citrate		
Σ aEq anions	128.7-139.4	158	159.18	165.15
Na/Cl	1.28 - 1.45	1.40	1.08	1.15
Glucose or others	3.9 - 5.6			
CO ₂	0.99 - 1.39			
pH	7.35 - 7.45		7.4	7.4
Σ aOsm	285 - 295	315	308	311.16
Use:		I.V. electrolyte therapy	Usually tissue culture, sometimes cardiac surgery	Biochemical experiments

2. a. 14. Delbecco R, Vogt M. *J Exp Med* 1954; 99: 167 - 1822. a. 13. *Facts and Comparisons* Oct, 1981, p.50, Lippincott, St.Louis2. a. 15. Krebs HA. *Hoppe S Z Physiol Chem* 1933; 217: 193

2g

Table I - Prior Art. Class 2b Solutions Containing 3 or 4 Cations, $\text{HCO}_3^-/\text{CO}_2$ and No Glucose or Other Non-Ionic Nutrients.

Units	Normal Plasma M.E.J.N. ----- 283, 1285 L fluid 1970	2. b. 1. Krebs Henseleit
Na	136 - 145	143
K	3.5 - 5.0	5.9
Ca free [Ca ²⁺] [1.06]	2.1 - 2.6	2.5
Mg free [Mg ²⁺] [0.53]	0.75 - 1.25	1.2
Σ aEq Cations	142.7-153.2	156.3
Cl	100 - 106	127.8
HCO_3	26 - 28	25
Σ Pi	1 - 1.45	1.18
SO_4	0.32 - 0.94	1.18
L - lactate	0.6 - 1.8	
pyruvate		
Lact/pyr		
D B OHbutyrate		
acetoacetate		
B HB/ acac		
acetate		
Other		
Σ aEq anions	128.7-139.4	157.3
Na/Cl	1.28 - 1.45	1.12
Glucose or others	3.9 - 5.6	
CO_2	0.99 - 1.39	1.24
pH	7.35 - 7.45	7.4
Σ aOsm	285 - 295	308
Use:	Multiple Biochemical Uses	

2. b. 1. Krebs HA, Henseleit K. *Hoppe-Seyle's Z Physiol Chem* 1932; 210: 33-66. This is the second major advance in fluids after S.J. Ringer, *Physiol* 1883; 4: 29, 223. This fluid became the basis for most tissue culture "balanced salt mixtures," was used in dialysis. It is known to contain twice too much Ca and Mg. It also has an abnormal Na/Cl ratio which Krebs himself unsuccessfully attempted to correct in 1950. (See Krebs HA. *B B A* 1950; 4: 249- 269, or Table I class 2d.)

Table 1 - Prior Art. Class 2c Solutions Containing 3 or 4 Cations, No $\text{HCO}_3^-/\text{CO}_2$ to Which is Added Non-Ionic Nutrients.

Units	Normal Plasma	2. c. 1. Lactated Ringer's	2. c. 2. 1/2 Strength Lact-Ringer	2. c. 3. Acetated Ringer's	2. c. 4. Ionosol B +5% Glucose (Abbott)	2. c. 5. Dianeal +1.5%Glucose (Travenol)	2. c. 6. Peritoneal Dialysis + 4.25%Glucose (Am. McGaw)	2. c. 7. Dianeal K14 +4.25%Glucose (Travenol)
mmoles -----	N.E.J.M. 283, 285	+ 5%Glucose	+2.5%Glucose	+ Glucose				
L fluid	1970							
Na	136 - 145	130	65	130	57	141	141.5	132
K	3.5 - 5.0	4	2	4	25			4
Ca free [Ca ²⁺]	2.1 - 2.6 [1.06]	1.5	0.75	1.5		1.75	2.0	1.875
Mg free [Mg ²⁺]	0.75 - 1.25 [0.53]				2.5	0.75	0.75	0.75
Σ mEq Cations	142.7-153.2	137	68.5	137	87	146	147	141
Cl	100 - 106	109	55	109	49	101	102.5	106
HCO_3^-	26 - 28							
Σ Pi	1 - 1.45				6.5 H_2PO_4^-			
SO_4	0.32 - 0.94							
L - lactate	0.6 - 1.8	29(d,l)	14(d,l)		25(d,l)	45(d,l)		35(d,l)
pyruvate								
Lact/pyr		00	00		00	00		00
D B OHbutyrate								
acetoacetate								
B HB/ acac								
acetate				28			44.5	
Other								
Σ mEq anions	128.7-139.4	137	69	137	87	146	147	141
Na/Cl	1.28 - 1.45	1.19	1.18	1.19	1.16	1.40	1.38	1.25
Glucose or others	3.9 - 5.6	278	139	278	278	83	236	236
CO_2	0.99 - 1.39							
pH	7.35 - 7.45					*5.5-6.5	*5.5-6.5	*5.5-6.5
Σ mOsm	285 - 295	524	263	523	443	366	510	494
Use:		I.V. fluid nutrition & electrolytes	I.V. fluid for de-hydration	same as 2.c.1.	Parenteral Nutrition	Peritoneal Dialysis	Peritoneal Dialysis	Peritoneal Dialysis

2. c. 1. Multiple Manufacturer's. Facts and Comparisons p.52, Oct 81

2. c. 2. Multiple Manufacturer's Facts and Comparisons p52, Oct 81

2. c. 3. Multiple Manufacturer's Facts and Comparisons p52, Oct 81

2. c. 4. (Abbott) Facts and Comparisons p52b, Aug '83

2. c. 5. (Travenol) Facts and Comparisons p704, Oct '82

2. c. 6. (American McGaw) Facts and Comparisons p704, Oct '82

2. c. 7. (Travenol) Facts and Comparisons p704, Oct '82

Table I - Prior Art. Class 2d Solutions Containing 3 or 4 Cations, Plus Non-Ionic Nutrients and $\text{HCO}_3^-/\text{CO}_2$

Units	Normal Plasma	2. d. 1.	2. d. 2.	2. d. 3.	2. d. 4.
mmoles	N.E.J.M.	Krebs	Tyrod's	Tyrod's	Locke's
-----	283, 1285	Serum	Solution 1	Solution	Solution
L fluid	1970	Substitute	(Schimassek)		
Na	136 - 145	141	151.54	150.1	157.57
K	3.5 - 5.0	5.93	5.9	5.9	3.57
Ca	2.1 - 2.6	2.54	1.8	1.8	2.16
free [Ca2+]	[1.06]				
Mg	0.75 - 1.25	1.18	0.45	0.45	0
free [Mg2+]	[0.53]				
Σ Eq Cations	142.7-153.2	154.37	162.07	160.5	165.46
Cl	100 - 106	104.8	147.48	147.48	163.92
HCO_3	26 - 28	24.9	11.9	11.9	3.57
Σ Pi	1 - 1.45	1.23	1.22	1.22	--
SO_4	0.32 - 0.94	2.36			
L - lactate	0.6 - 1.8		1.33		
pyruvate		4.9	0.09		
Lact/pyr			14.8		
D B OHbutyrate					
acetoacetate					
B HB/ acac					
acetate					
Other		2.45 glutamate ⁻ 5.4 fumarate ²⁻			
Σ aEq anions	128.7-139.4	154.47	162.81	161.6	167.49
Na/Cl	1.28 - 1.45	1.35	1.03	1.02	0.96
Glucose	3.9 - 5.6	9.2	5.45	5.6	5.6 - 13.7
or others					
CO_2	0.99 - 1.39	1.0	1.17		
pH	7.35 - 7.45	7.4	7.1	7.1	?
Σ mOsm	285 - 295	308.2	328	318.3	336
Use:		Artificial Liver Serum for Perfusion Tissue Slices Normal Na/Cl			

2. d. 1. Krebs HA. *B.B.A.* 4: 249 - 269, 1950. Not used *in vivo* but presented for comparison of composition.
2. d. 2. Tyrod's solution as modified for liver perfusion by Schimassek H, *Biochem Z* 338: 460, 1963. Not used *in vivo* but presented to show prior art in composition. Same for 2.d.3, Tyrod's, and 2.d.4, Locke's.
2. d. 3. Tryrod MV, *Arch int Pharmacodyn Ther* 20: 205 - 223, 1910.
2. d. 4. Locke FS, *Zentbl Physiol* 14: 670 -672, 1900.

1 Contemporarily, a large number of different
aqueous electrolyte solutions are prepared, sold in com-
merce, and used as in vivo fluids, such as for electro-
lyte and fluid replacement, parenteral nutrition, and
5 dialysis (both hemo-and peritoneal).

Even a cursory examination of Table I will confirm
the medical dicta that "plasma is an unmakeable solution".
The solutions listed in Table I illustrate this belief.
The essential problem is that plasma contains, in addi-
10 tion to major inorganic electrolytes, trace quantities
of various electrolytes plus various metabolites includ-
ing plasma proteins. In practice, it has not been possible
to construct synthetically a replication of plasma
because of its complexity. Blood, extracellular fluid,
15 and even plasma can be regarded as tissues.

In most prior art electrolyte solutions, the con-
centration of chloride anions (Cl^-) is higher than in
human plasma or serum. For example, the Krebs Henseleit
solution (see Table I) contains a concentration of Cl^-
20 which is about 20% higher than in human serum. This
anion gap, that is, the difference between the positive
cations and the negative anions, is now known to be due
largely to the anionic metabolites in normal plasma
plus the contribution of acidic amino acid groups found
25 on plasma proteins. Referring to Table I, it is seen
that the total positive cations in plasma is 142-154
meq/l while the total anions is only about 128-137 meq/l
leaving a deficit of about 14-17 meq/l of anions. For
convenience, the anion gap in human plasma can be ex-
30 pressed as the ratio of sodium cation milliequivalents
per liter to chloride anion milliequivalents per liter.

From Table I, it is clear that the Krebs Serum
substitute (Krebs, H.A. Biochem, Biophys. Acta 4, 249-
269, 1950) comes closest to approximating the electro-
35 lyte composition of human plasma. In this solution,

1 Krebs attempted to correct the excessive Cl^- content
in Krebs Henseleit solution (Hoppe-S. Z. Physiol. Chem.
210, 33-66, 1932) using metabolic experiments with tissue
slices. Because of the law of electrical neutrality,
5 Na^+ cannot be added to a solution without some anion
(such as Cl^-) being added also; the sum of cations and
anions must be equal in any solution. In his 1950
attempt, Krebs chose pyruvate $^-$, l-glutamate $^-$, and
fumarate $^{2-}$ as anions to be added.

10 An alternative to Krebs selection of anions came
about at the same time. In 1949, the use of high concen-
trations of acetate as a metabolizable organic anion was
advocated (Mudge G.H., Mannining J.A., Gilman A.;
Proc. Soc. Exptl. Biol. Med. 71, 136-138, 1949). This
15 idea led in 1964 to the advocacy of the use of 35-45mM
(millimolar) acetate in commercial hemodialysis
fluids (Mion C.M. Hegstrom R.M., Boen S.T., Scribner
B.H.; Trans. Am. Soc. Artif. Internal Organs 10, 110-113,
1964).

20 In addition to the above organic anions, the current
reference work "Facts and Comparisons" indicates various
commercial electrolyte fluids which contain lactate
anion.

All of the prior art electrolyte solutions (with
25 or without nutrients) as exemplified in Table I are now
believed to lead to undesirable and pathological conse-
quences particularly through extended usage. As regards
acetate, editorials recently appearing in the British
Medical Journal, 287, 308-309, 1983) present evidence
30 that acetate leads to fatigue, nausea, malaise, sudden
hypotension, increased atherosclerosis, hypoventilation,
and hypoxia. Also, the originator of acetate dialysis now
advocates its use only in "healthy" patients (Pagel
M.D., Ahmed S. Vizzo J.E. and Scribner B.H.; Kidney Int.
35 21, 513-518, 1982).

1 Krebs choice of glutamate⁻ and fumarate²⁻ is incor-
rect because these anions do not penetrate cell membranes
in a predictable manner, but, like citrate³⁻, exhibit
severe gradients of six fold or greater between plasma
5 H₂O and cell H₂O. The alternate use of d,l-lactate⁻
(Hartmann AF. J Am Med Asso 103 1349-1354, 1934) is now
known to induce severe abnormalities, particularly coma
at levels far below the 28 to 35 mM d,l-lactate contained
in these solutions (Oh MS et al, N. Eng J Med 301 249
10 251, 1979; Stolberg L, et al N Eng J Med 306: 1344-1348.
1982; Ballabriga A, et al Helv Paediatr Acta 25:25-34,
1970) in to the induction severe abnormalities in redox
and phosphorylation state induced by the use of l-lactate
alone. The use of gluconate⁻ induces abnormalities
15 in the hexosemonophosphate pathway. Indeed, all previous
used organic ions violate the "safe entry points" or
the normal Na:Cl ratio as herein defined.

 In addition to the use of d,l-lactate, gluconate,
fumarate, glutamate, pyruvate, and citrate anions in
20 current commercially available prior art electrolyte
fluids, and wherein such anions are typically employed
at levels above those found in the (plasma or serum)
of healthy humans, many such prior art commercial fluids
also employ high levels of nonionic metabolites, such as
25 fructose and glycerol, which induce separate redox
state and phosphorylation potential abnormalities in
phosphorylation potential with rapid destruction of
liver purine nucleotides and their release into blood
sometimes leading to renal shutdown due to uric acid
30 deposition in the kidneys (see Woods H.F., Eggleston
L.V. and Krebs H.A.: Biochem. J. 119, 501-510, 1970).
Fructose in plasma above 0.2mM must be considered to
violate the "safe entry point". Likewise, use of intra-
venous glycerol at levels above 5mM/l as currently
35 practiced leads, in tissue containing glycerol kinase,

1 such as kidney and liver, to accumulation of 10 mM
glycerol phosphate (over 100 times normal). See Bruch
H.B. et al.: J. Biol. Chem. 257, 3676-3679, 1982).

5 In addition to failing to solve the anion gap
problem (or to provide a normal milliequivalent ratio
of sodium cation to chloride anions) without causing
profound and adverse physiological effects (including
disruption of normal redox state and normal phosphoryl-
10 ation potential), many prior art aqueous electrolyte
solutions for in vivo usage fail to have a pH which
approximates the pH of mammalian intracellular and
extracellular fluids, especially plasma or serum.

Mammalian systems normally operate at temperatures
between about 37-38°C where, by common thermodynamic
15 convention, neutral pH is taken to be about 7 at 25°C.
It is clear that changes in pH, (the negative log
10 of $[H^+]$ concentration) necessarily affect the
fundamental energetic relationships occurring in
living cells. Also, enzymes have sharply defined ranges
20 of $[H^+]$ concentration in which they perform their
catalytic functions in a normal manner. Deviation of
mammalian plasma pH down to 6.9 or above 7.7 from its
normal range of 7.35 - 7.45 is therefore fatal to most
mammalian organisms. Massive changes in the cellular
25 redox and phosphorylation states also disorder cellular
homeostasis.

The pH of human plasma is normally maintained by
the human body in the range from about 7.35 to 7.45
while the pH of human cellular cytoplasm is about 7.2
30 (see Veech et al in J. Biol. Chem. 254, 6538-6547, 1979).
If blood pH drops to 6.8 in man, then death ensues from
cardiac arrest, and if blood pH increases to above pH
7.7, then death ensues from convulsions.

The major chemical system maintaining body pH
35 within this narrow normal range is the $[CO_2]/[HCO_3^-]$

1 buffer system. The $[\text{CO}_2]$ of blood is maintained minute
to minute by a portion of the mammalian brain called the
respiratory center which senses brain cell pH and adjusts
the depth and speed of respiration to change pH by increas-
5 ing or decreasing $[\text{CO}_2]$ according to the famous Henderson
Hasselbalch equation (Henderson L.J., Silliman Lectures,
Yale U. Press, New Haven, 1928).

Even though pH is thus seen to be a critical factor
in mammalian blood, many commercial electrolyte solutions
10 as administered have pH values which deviate substantially
from normal. Others give excessive Cl^- relative to Na^+
which results in hyperchloremic acidosis, (Black D.A.K.:
Lancet i 305-12, 1953), or give organic anions in a
manner which causes measurable deviations from normal
15 in the metabolic processes of the cell. Also, many
commercially available electrolyte solutions contain
no carbon dioxide which can result in a loss of
respiratory drive and consequent hypoxia in patients.

The compositions and methods of the present inven-
20 tion overcome the above indicated prior art problems.
These compositions and methods employ definite ratios
of $[\text{bicarbonate}^-]/[\text{carbon dioxide}]$, $[\text{l-lactate}^-]/$
 $[\text{pyruvate}^-]$, and $[\text{d-betahydroxybutyrate}^-]/[\text{acetoacetate}^-]$.
Each of these mixtures constitute a near equilibrium
25 couple which is known to be a normal constituent of
mammalian plasma. While each of these pairs of
components has been previously employed at least on a
laboratory basis in solutions used for animal (mammalian)
experiments, these mixture pairs have never previously
30 been used in an electrolyte solution to obtain a normal
 $\text{Na}:\text{Cl}$ milliequivalent ratio or to solve the anion gap
problem.

All previous electrolyte solutions, and plasma
substitutes, induce severe and measurable pathogenic
35 abnormalities and no prior art electrolyte solution or
plasma substitute has both (a) employed at least one

1 of the three mixture pairs of this invention and (b)
achieve a normal Na: milliequivalent ratio as taught
herein. Thus, for example, the Krebs Henseleit solution
contains the $[\text{HCO}_3^-]/[\text{CO}_2]$ buffer system (but contains
5 excessive chloride ions). Schimassek (Schimassek H.;
Bio. Chem. Z. 336, 460, 1963) added about normal blood
levels of lactate and pyruvate to what is essentially
Tyrode's solution (see Tyrode, M.J.: Arch. Int. Pharma-
codyn 20, 205, 1910) containing 2.5% albimin in an attempt
10 to create a physiological solution for perfusion. It
should be noted that Schimassek added 1.33mM/L D-
L-lactate, which is definitely abnormal (see normal
blood lactate levels shown in Table 1). Further, the Na^+
of 151mM/l and Cl^- of 147.5mM/l in Schimassek's modified
15 Tyrode's solution approximates the concentration of
155mM/l Na and 155mM/l Cl in so-called normal (0.9%)
saline, the most widely used electrolyte infusion solution,
and thus obtained a grossly abnormal Na:Cl milliequivalent
ratio of about 1.24 - 1.45 with a mean of about 1.38.
20 Infusions of electrolyte solutions with a Na:Cl milli-
equivalent ratio of less than about 1.38 have long been
known to cause hyperchloremic acidosis in the treated
organism. (See Levinsky N.G. in Harrison's Textbook
of Medicine pp 230-236, McGraw-Hill, N.Y., 1983). It
25 is the attempt to avoid this problem that leads to the
wide use of such solutions as Ringer's lactate or acetate
dialysis fluids which overcome the Na:Cl ratio problem,
but which in turn create gross abnormalities of other
types. It is the attainment of a normal Na:Cl milli-
30 equivalent ratio in a manner which avoids the pathologi-
cal consequences inherent in all currently known or
practiced methods which is a major part of the invention
herein disclosed.

The making of a Krebs Henseleit electrolyte solu-
35 tion (or other prior art electrolyte solution) and the

1 incorporation therein of a mixture of L-lactate and
pyruvate anions, or of a mixture of D-betahydroxybutyrate
and acetoacetate anions did not, and could not, result
5 in the making of an electrolyte solution wherein the
anion gap problem was overcome (or wherein the milli-
equivalent ratio of sodium cations to chloride anions
was normalized), in accordance with the teachings of the
present invention, because each of such resulting solu-
10 tions would still contain excessive chloride anions and
so would inevitably cause hyperchloremia if and when
used in human or mammalian therapy.

In general summary, the prior art describes a series
of electrolyte solutions typically of about 270-320
milliosmoles (or higher) comprised of: (a) 1 to 4
15 metallic cations of sodium, potassium, magnesium, and
calcium in amounts greater than 0.5mM/L, (b) 1 to 5
inorganic anions of chloride plus also HPO_4^{2-}),
(c) 0 to several organic carboxylic or bicarbonate
anions, (d) 0 to 5 nonionic materials in concentrations
20 of greater than about 0.5mM/L from the group comprising
 CO_2 gas, glucose, urea, glutamine, and others,
and (e) sometimes one or more high molecular weight
substances, such as albumin, hemocel, and the like.
None of these solutions, for the reasons herein above
25 explained, either normalize the milliequivalent ratio
of Na:Cl at all, or normalize this ratio without
causing profound and adverse physiological consequences.
In the present invention, there are provided processes
and compositions of a complex fluid nature for in vivo
30 usage which can substantially completely eliminate
all of such prior art problems. While the components
of these new solution compositions are known solution
components, no one has heretofore formulated the
solutions of the present invention which not only
35 tend to achieve a normal plasma milliequivalent ratio

1 of sodium cations to chloride anions, but also tend to
achieve a normalization of plasma pH and a normalization
of the cellular redox state and the cellular phosphoryla-
tion potential. Also, these new solutions permit one
5 to avoid usage of the previously employed carboxylic
anions, as acetate, or lactate alone, which cause
adverse effects.

BRIEF SUMMARY OF THE INVENTION

This invention relates to processes for
10 accomplishing electrolyte and water therapy while simul-
taneously normalizing blood composition in a mammal
(including man) by introducing in a physiologically
effective amount by any means, including parenterally,
(intravenously), intra-arterially, intramuscularly,
15 intravascularly, and the like, by dialysis, or orally,
and the like into such mammal an aqueous solution wherein:

- (a) the ratio of sodium cation milliequivalents per
liter to the chloride anion milliequivalents
per liter are so selected as to tend to produce
20 the range found in normal mammalian blood plasma,
- (b) there is a physiologically effective amount of
at least one near equilibrium couple selected
from the group consisting of
 - (1) bicarbonate⁻ and carbon dioxide,
 - 25 (2) l-lactate⁻ and pyruvate⁻, and
 - (3) d-betahydroxybutyrate⁻ and acetoacetate⁻, and
- (c) the pH ranges from 5 to 9.

This invention further relates to physiologically
compatible aqueous salt solutions for mammalian (includ-
30 ing human) administration which contain such a ratio
of sodium to chloride and which incorporate near-equili-
brium couple(s).

This invention provides electrolytes of the class
indicated wherein physiologically normal concentrations
35 of the divalent cations Mg^{2+} and Ca^{2+} may be included

1 without precipitation. No one has previously made solutions for in vivo use which contain the correct Na^+Cl^- ratio and which also contain the physiologically normal respective amounts of Mg^{2+} and Ca^{2+} .

5 When used for mammalian administration in accord with the present process teachings, such a solution:

- (a) tends to maintain and normalize in plasma the milliequivalent ratio of sodium cations to chloride anions in the normal range, and
- 10 (b) tends to maintain and normalize plasma pH, and
- (c) tends to maintain and normalize the redox state and the phosphorylation potential.

One (first) class of such solutions characteristically utilizes (contains) an inorganic class of anions comprised of chloride and bicarbonate. These solutions have a physiological pH which is broadly in the range from about 5 to 9, and preferably in the range from about 6.9 to 8.6, and more preferably in the range from about 7.35 to 7.45, and most preferably is about 7.4 (for human use). Dissolved carbon dioxide is also present in these solutions. When administered, these solutions not only tend to maintain the treated mammal's normal blood (and plasma) ratio of sodium to chloride, but also tend to set (regulate) the treated mammal's blood (plasma) pH at a normalized value. In addition the treated mammal's redox state and phosphorylation potential tend to be normalized.

Another (second) class (preferred) of such solutions characteristically utilizes (contains) chloride anions and a class of carboxylate anionic mixture couples comprised of at least one member from the group consisting of (a) a mixture of l-lactate⁻ anions and pyruvate⁻ anions, (b) a mixture of d-betahydroxybutyrate⁻ anions and acetoacetate⁻ anions, and (c) a mixture of both (a)

35

1 and (b). These solutions have a physiological pH which
is as above defined in connection with such (first)
class of solutions. When administered, these solutions
not only tend to maintain the treated mammal's redox
5 state within a normal range, but also tend to maintain
that mammal's phosphorylation potential within a normal
range.

Another (third) class (more preferred) of such solu-
tions characteristically utilizes (contains) both chloride
10 anions, and bicarbonate/carbon dioxide mixture, as in
such (first) class of solutions, but also utilizes
(contains) such class of carboxylate anionic couples,
as in such (second) class of solutions. When admini-
stered, these solutions achieve the above indicated
15 effects obtained from the use of such (first) class of
solutions and the above indicated effects obtained from
the use of such (second) class of solutions.

The specified milliequivalent ratio of sodium to
chloride in normal mammalian blood generally is believed
20 to be in the range from about 1.24:1 to 1.47:1. In
the case of a normal human adult, this range is now
believed to extend (based on published information)
from about 1.24:1 to 1.45:1 and preferably from about
1.33:1 to 1.42:1 and most preferably from about 1.36:1
25 to 1.42:1. These ratios of $\text{Na}^+:\text{Cl}^-$ are typically employed
in solutions used in the practices of this invention.
Ratios above 1.47, i.e. from about 1.47 to about 1.6 can
be used within the spirit and scope of this invention as
when it is the physician's conscience intention to create
30 an abnormal $\text{Na}^+:\text{Cl}^-$ ratio as, for example, to create an
excess of alkali reserve; however, such higher ratios
are generally not presently preferred for general usage.
In the case of dialysis fluids or to create an alka-
lotic condition in a cell or to correct an existent
35 acidosis, this $\text{Na}^+:\text{Cl}^-$ ratio could range from a normal
value (about 1.24 to 1.45) to about 1.6.

1 In using these couples, the important factor is
the ratio of the concentration of [product] / [reactant]
(see Eqns 0, 1,2,3,4,5 & 7 hereinbelow). The absolute
concentration becomes important in affecting the chemical
5 activity of water (e.g. the osmotic pressure).

The total quantity, or sum (σ), of each of
the couples (bicarbonate / CO_2 , l-lactate / pyruvate,
and d-betahydroxybutyrate / acetoacetate) present in a
solution of this invention can range from 0 to about 465
10 mMoles/liter of solution. However, in routine situa-
tions, the quantity of each couple commonly ranges from
0 to about 25 to 60 mMoles/liter.

Preferably, the ratio of bicarbonate milliequivalents
per liter to dissolved carbon dioxide milliequivalents
15 per liter in a solution of this invention can range
from about 0.1:1 to 55:0.1 and preferably 11:1 to 24:1.
More preferably, such total ranges from about 10 to 45
mM/l and such ratio ranges from about 18:1 to 26:1,
and still more preferably such total ranges from about
20 23 to 35 mM/l while such ratio ranges from about 19:1
to 21:1. A ratio of 19.95 for $[\text{HCO}_3^-]/[\text{CO}_2]$ gives a pH
7.4, which is presently particularly preferred.

Preferably, the ratio of l-lactate anion milli-
equivalents per liter to pyruvate anion milliequivalents
25 per liter in a solution of this invention can range from
about 20:1 to 1:1. Preferably, such total quantity
ranges from about 0.5 to 10 mM/l and such ratio ranges
from about 3:1 to 15:1, and more preferably such total
quantity ranges from about 2 to 8 mM/l while such ratio
30 ranges from about 5:1 to 12:1.

Preferably, the ratio of d-betahydroxybutyrate anion
milliequivalents per liter to acetoacetate milliequivalents
per liter in a solution of this invention can range from
about 6:1 to 0.5:1. Preferably, such total ranges from
35 about 1 to 10mM/l and such ratio ranges from about 4:1 to

1 1:1, and more preferably such total ranges from about 2
to 5mM/l while such ratio ranges from about 3:1 to 1.5:1.

By the term "milliequivalent ratio" as sometimes
used herein, reference is had the ratio of milliequivalents
5 per liter of one substance to milliequivalents per liter
of another substance in an aqueous medium.

One of the three near equilibrium couples employed
in the practice of this invention (the bicarbonate⁻/
carbon dioxide couple) tends, as used in this invention,
10 to regulate the concentration of hydrogen ions in blood
(plasma) and in the treated mammal's cells, and each one
of such couples tends to normalize the redox state of
each of the three pyridine nucleotide couples. The
phosphorylation potential also tends to be normalized.
15 Also, each such near equilibrium couple when used as
herein described constitutes a safe entry point into
the metabolic system of a mammal.

By the term "safe entry point" as used herein refer-
ence is generally had to a metabolite which, in living
20 tissue or cells:

- (1) does not cause a massive buildup of one or
more of intermediate cellular metabolites,
- (2) does not cause a severe disruption of any one
of the controlling nucleotide ratios in a
25 living cell,
- (3) can be added to a physiological system of a
living mammal at a concentration level which is
greater than that which is found normally in
such system (such as blood plasma of a fasting
30 mammal) without causing any appreciable
distortion in metabolism and without causing any
pathological conditions to arise, and
- (4) may be found in normal variants of the
physiological state as when the total of d-
35 betahydroxybutyrate plus acetoacetate reaches

1 a level of about 8 to 10 mM/l in three- day
fasting man, or the total of l-lactate plus
pyruvate rises to a level of about 5 to
6 mM/l in a jogging normal man.

5 Further, each such above described near equilibrium
couple in this invention exhibits a distribution or
permeability between intracellular fluid and extra-
cellular fluid such that the ratio of the concentrations
in, respectively, intracellular fluid to extracellular
10 fluid ranges from about 1.0:1 to 1.5:1 in most all
mammalian cells.

These respective three pairs of permeant mono-
carboxylate near equilibrium couples are unique among
metabolites in being osmotically neutral in respect
15 to the water in intracellular and extracellular space.
Administration of these three couples, as their appro-
priate cationic salts (individually or in some combina-
tion with one another as taught herein) necessarily re-
sults in no net change in the distribution of water
20 between intracellular and extracellular spaces in most
tissues. By administration of varying ratios of these
couples, however, the physician may control the distri-
bution of water by varying the redox state and hence the
phosphorylation state as described in equation 7 herein
25 below. Osmotically active substances incorporated with
the solutions of this invention preferably should each
constitute a safe entry point. For example, glucose
above 13mM/l is higher than ever occurs under normal
physiological conditions in a healthy man. Use of
30 glucose above 13mM/l (as in the widely used 5% glucose
solution) as a calorie source is, apart from consideration
of the source of pathology, and apart from the carbox-
ylate couples, considered herein to be an acceptable
source of calories. The extreme ability of the
35 mammalian body to regulate its glucose metabolism makes

- 1 it far to be preferred over other possibly nonionics,
 such as fructose or glycerol, which enter the metabolic
 system in an uncontrolled manner causing pathologic changes
 such as are already referenced, and so such are not
 5 safe entry points.

Characteristically, a solution used in the practice
 of this invention can contain from about 1 to 2400
 millimoles per liter of sodium cations, but, in routine
 situations, commonly ranges from about 120 to 170 mM/l
 10 and more preferably from about 129 to 163.5mM/l and most
 preferably from about 136 to 145mM/l.

In addition, a solution contains sufficient chloride
 anions to produce a milliequivalent ratio of sodium
 cations to chloride anions in the range above defined.

- 15 Optionally, in addition to sodium, a solution of
 this invention can contain one or more of the following
 additional metallic cations each in a respective quantity
 as below indicated:

Table II

cation component	Quantity range (millimoles per liter)		
	broad	preferred	more preferred
potassium	0 - 90	0 - 40	0 - 5
calcium	0 - 60	0 - 10	0 - 1.5
25 magnesium	0 - 15	0 - 10	0 - 1

- Optionally a solution of this invention can have
 additionally incorporated (dissolved) therein from 0 to
 about 2400 millimoles per liter of at least one osmotical-
 ly active substance which is preferably metabolizable
 30 and preferably substantially nonionic (including
 zwiterionic).

A solution used in the practice of this invention
 is further characterized by generally having:

- (1) sufficient total substances dissolved therein to
 35 produce an osmolarity ranging from about 260 to
 5000 milliosmoles/liter (mOs), and preferably

from about 265 to 550 mOs, and more preferably from about 280 to 320 in mOs, and most preferably about 311 milliosmoles/liter.

- (2) the relationship between total (dissolved) ionic substances is such that the pH ranges from about 5 to 9, and preferably from about 6.9 to 8.6; and most preferably from about 7.35 to 7.55;
- (3) the charges of all cations equal the charges of all anions; and
- (4) the minimum total concentration of all such near equilibrium couples(s) present is at least about 0.1 millimoles per liter, and preferably is at least about 0.5 mM/l, and more preferably about 2 mM/l, while the maximum concentration thereof is preferably not more than about 465 mM/l and more preferably is not more than about 65 mM/l and most preferably is not more than about 50 mM/l.

Examples of usable osmotically active substantially nonionic substances include glucose, glycerol, fructose, sorbitol, and the like. Glucose is presently most preferred.

As hereinbelow explained, the processes and the solutions of the present invention find use in a wide variety of therapeutic applications, such as in electrolyte and fluid replacement, parenteral nutrition, and dialysis.

Various additional objects, aims, purposes, features, advantages, applications, variations and the like will be apparent to those skilled in the art from the teachings of the present specification taken with the claims.

1

DETAILED DESCRIPTION

This description is based upon best available information (including theory) known to the inventor. Any misdescription or the like, if such should exist, is not believed to alter the fundamentally correct basis and evidence supporting the present invention.

5

A. The Redox State

In biological cells, most reactions are catalyzed by enzymes of which an average cell may have of the order of 10^4 . In one classification, enzymes may be grouped in only six functional categories.

10

15

20

25

30

35

- (1) dehydrogenases which transfer H^+ and e^- from one substrate to another by the use of cofactors, such as NAD^+ (nicotinamide adenine dinucleotide), or prosthetic groups, such as FAD (flavin adenine dinucleotide), or others;
- (2) kinases or phosphotransferases which effect the group transfer of a phosphate to a substrate usually by using a co-factor, such as ATP or other similar phosphate-containing compounds;
- (3) carbon-carbon bond group transferases which either or break carbon-carbon bonds using cofactors of the co-enzyme A type or occur on a solid state substrate, such as a glycogen particle, or the surface of a fatty acid synthase multi-enzyme complex;
- (4) isomerases which effect internal rearrangements within a compound;
- (5) hydratases which either add or subtract water from a substrate; and
- (6) peptidases which break C-N bonds or create such bonds again usually taking advantage of a solid state synthetic matrix, such as a ribosome.

1 A special class of substrates taking part of biological
reactions catalyzed by enzymes are called co-factors or
co-enzymes. Co-enzymes, such as, for example, NAD,
become attached and detached from an enzyme during a
5 catalytic cycle, while prosthetic groups, such as flavin
nucleotides or cytochromes, remain firmly attached
during the catalytic cycle.

Since co-enzymes take part in multiple intra-
cellular reaction within a given cellular compartment,
10 the chemical potential of the co-enzyme couple becomes of
central importance in energy transformation and oxido-
reductions occurring in living matter. The thermodynamic
characteristics of a particular whole set of oxido-reduction
reactions is dependent upon the ratio of the free
15 concentrations (strictly speaking, the activities) of
the free $[NAD^+]$ and free $[NADH]$ ratio. The ratio
 $[NAD(P)^+]/[NAD(P)H]$, thus represents and defines the
redox state, at a given pH, of a particular pyridine
nucleotide couple, and this ratio then determines:

- 20 (1) the extent and direction of reversible
reactions in near-equilibrium with that co-
enzyme couple;
- (2) The extent to which a co-enzyme couple can be
effective as an intracellular reducing agent,
25 for example, in reducing the beta-oxpacyl co-
enzyme A to beta-hydroxyacyl-coenzyme A; and
- (3) the magnitude of the free-energy changes of
oxido-reductions in the electron transport
chain responsible for the major portion of
30 ATP synthesis.

The term "redox state" as thus used herein can be
considered to refer to the oxidation-reduction state of
any one or more of the three main pyridine nucleotide
couples. Each of these couples are:

- 35 (A) The cytoplasmic $[NAD^+]/[NADH]$ linked

1 dehydrogenase reactions of: (1) Lactate
dehydrogenase (EC 1.1.1.27); (2) Malate
dehydrogenase (EC 1.1.1.37); and (3) Glycerol
3-phosphate Dehydrogenase (EC 1.1.1.8).

5 (B) The mitochondrial $[NAD^+]/[NADH]$ linked
dehydrogenase reactions of: (1) Beta
hydroxybutyrate dehydrogenase (EC 1.1.1.30);
and (2) Glutamate dehydrogenase (EC 1.4.1.3).

10- (C) The cytoplasmic $[NADP^+]/[NADPH]$ linked
dehydrogenase reactions of: (1) Isocitrate
dehydrogenase (EC 1.1.1.42); (2) 6-
Phosphogluconate dehydrogenase (EC 1.1.1.44);
and (3) Malic Enzyme (EC 1.1.1.40).

The three pyridine nucleotide couples or pools
15 each achieve different redox potentials because of the
chemical energies of the substrates to which they are
linked by their respective enzymes since the standard
redox potential of $[NAD^+]/[NADH]$ is about -0.32V. Thus,
the near-equilibrium NAD-linked dehydrogenases have a
20 Keq of about $10^{-11}M$, the mitochondrial NAD-linked dehydro-
genases have a Keq of about $10^{-9}M$, and the cytoplasmic
NADP linked dehydrogenases have a Keq of about 1. The
differences in pyridine nucleotide redox states within
the cell may be considered to result from the fundamental
25 properties of matter. Over time, enzymes have evolved
which take advantage of these fundamental properties to
organize the chemical reactions of the cell into co-
herent purposeful sequences we know as metabolism.

The oxidation of lactate anions to pyruvate anions
30 (that is, the loss of $2H^+$ and $2e^-$ from lactate) is accom-
panied by the reduction of pyridine nucleotide NAD^+ .
That is, NAD^+ gains two electrons and one H^+ with the
other H^+ being liberated into the aqueous media where
its activity is indicated and controlled by the
35 HCO_3^-/CO_2 couple.

1 In general, the term "redox state" may also be
defined as a ratio of [oxidized substrate]/reduced sub-
strate]. The half or mid point potential E_h is convention-
ally measured as a potential in volts relative to a
5 standard hydrogen electrode potential in accordance with
the Nernst equation. The mid point potential of the NAD^+
system, that is, where the ratio of $[\text{NAD}^+]/[\text{NADH}]$ equals
1 at a pH of 7.0 and a temperature of 25 C is -0.32 volts
10 under standard conditions. The midpoint potential of
 $[\text{O}_2]/\text{H}_2\text{O}]$ is +0.816 volts. The cytoplasmic pyridine
nucleotide system accepts H^+ and e^- from the organic
compounds provided to mammalian organisms and transfers
them to the mitochondrial pyridine nucleotide system where,
by the electron transfer system, the $2\text{H}^+ + 2\text{e}^-$ reduce
1/2 O_2 to form water while conserving the energy of the
oxidation reduction reaction by converting ADP + Pi
to ATP. The reaction generates energy and heat. The
redox state of cytoplasmic $[\text{NAD}^+]/[\text{NADH}]$ couple is about
-0.19 volts, that of the mitochondrial $[\text{NAD}^+]/[\text{NADH}]$
20 couple is about -0.28 volts while that of the cytoplasmic
 $[\text{NADP}^+]/\text{NADPH}]$ couple is about -0.42 volts. The last
or NADP^+ couple is a much stronger reducing agent than
the others and is used for reductive synthesis in the
body, such as the making of fatty acids from carbohydrates;
25 (see Krebs and Veech, 1969) in The Energy Levels and
Metabolic Control in Mitochondria (Papa S., Tager J.R.,
Quagliariello E. & Slater E.C. eds) pp 329-382,
Adriatica Editrice, Bari.

 In the case of a living cell, a plurality of oxi-
30 dation-reduction reactions occur simultaneously. Under
normal conditions, these reactions occur in a normal
healthy cell in a predictable manner. How these various
redox states are regulated has just been described in
thermodynamic terms. The normal healthy cell keeps the
35 redox state of its free cytoplasmic $[\text{NAD}^+]/[\text{NADH}]$ redox

1 couple at a ratio of about 500 to 1500 which corresponds
to a voltage of about -0.2 volts. In this way, the cyto-
plasmic pyridine nucleotides can accept the H^+ and e^-
from the substrates or food presented to the cell so
5 that the cell may convert this food or substrate into
energy. When the cell is metabolizing very reduced sub-
strates, such as fatty acids, the cytoplasmic
[NAD^+]/[NADH] is about 400-800. When the cell is meta-
bolizing carbohydrates or amino acids, it is obvious that
10 these compounds are already partially oxidized. There-
fore, the free cytoplasmic [NAD^+]/[NADH] reflects the oxi-
dation level of its substrate and becomes more oxidized
in the range of about 800 to 1500.

The redox state of the free cytoplasmic [NAD^+]/
15 [NADH] couple can be determined by various techniques,
such as by measuring the ratio of [lactate $^-$]/[pyruvate $^-$]
(a) in freeze clamped tissue, (b) in the venous effluent
leaving the organ in question, or (c) in the medium
bathing the tissue in question. Alternatively [L-
20 malate $^-$]/[oxaloacetate $^-$] or [-glycerophosphate]/
[dihydroxyacetone P] ratios in tissue may be measured,
if desired. The value of cytoplasmic [NAD^+]/[NADH]
can then be calculated.

In healthy living mammals, the ratio of [L-lactate $^-$]
25 /[pyruvate $^-$] is about 6, but can range, under special
situations, such as starvation, to about 15 - 20. A
[L-lactate $^-$]/[pyruvate $^-$] ratio below about 20, as occurs
after ethanol consumption, because of its links to the
cytoplasmic [NAD^+]/[NADH], is pathologic. A character-
30 istic in all cells having a low [NAD^+]/[NADH] ratio is
believed to be demonstrable (observable) pathologic
consequences, such as tissue swelling, low
phosphorylation potential, low plasma membrane voltage,
and abnormal electrolyte distribution between intra-
35 cellular and extracellular H_2O .

1 Similarly, the redox state of the free mito-
chondrial $[NAD^+]/[NADH]$ can be determined by various
techniques using tissues such as, for example, kidney or
liver, by measuring the ratio of $[D\text{-}\beta\text{-hydroxybutyrate}^-]$
5 $/[acetoacetate^-]$ (a) in freeze-clamped tissue, (b) in
the venous effluent leaving such tissue, or (c) in the
fluid bathing isolated such tissues. A determination of
the free mitochondrial $[NAD^+]/[NADH]$ in other tissues,
such as brain or heart muscle, is more complex, but, in
10 some cases, can be accomplished by measurement in freeze
clamped tissue of the $[\alpha\text{-keto glutarate}^-] [NH^+]/$
 $[glutamate^-]$ ratio (see Miller A.L., Hawkins R.A., and
Veech R.L.; J. Neurochem 20, 1393-1400, 1973).

 The normal ratio of mitochondrial $[NAD^+]/[NADH]$ is
15 between about 50 and 20, and the normal ratio of $[\beta\text{-hydroxybutyrate}^-]/[acetoacetate^-]$ is about 1.3 to 4.
The value of mitochondrial $[NAD^+]/[NADH]$ can then be
calculated.

 The redox state of the free cytoplasmic
20 $[NADP^+]/[NADPH]$ couple is, of course, affected by the
 $[CO_2]$ of surrounding fluids. Because of the lack of
substrates which are permeable to the cell wall without
significant and variable gradients, this redox state
cannot at present be directly and totally regulated other
25 than by the intracellular metabolic links with the
cytoplasmic and mitochondrial $[NAD^+]/[NADH]$. (See Krebs
H.A. and Veech R.L.; "Pyridine Nucleotide Interrelations",
1969 in The Energy Level and Metabolic Control in
Mitochondrial in Papa S., Tager J.M., Quagliariello E.,
30 and Slater E.C., eds. pp 329-383, Adriatic Editrice,
Bari). Thus, for instance, because pyruvate reacts
in both cytoplasmic $[NAD^+]/[NADH]$ and $[NADP^+]/[NADPH]$,
administration of $[HCO_3^-]/[CO_2]$ and $[L\text{-lactate}^-]$
 $[pyruvate^-]$ within certain narrow limits regulates these
35 ratios because:

$$\frac{[NAD^+]_c}{[NADH]_c} = \frac{[NADP^+]_c}{[NADPH]_c} = \frac{K_{\text{malic enzyme}} \times [\text{malate}^{2-}]}{K_{\text{LDH}} \times [\text{L-lactate}^-] [\text{CO}_2]}$$

Pyruvate, L-lactate and CO_2 are permeable to cell wall in a simple fashion, as are D-betahydroxybutyrate and acetoacetate, while malate²⁻ and other dicarboxylates are not.

While the importance of redox state to the maintenance and normalization of intracellular metabolic processes and bioenergetics has long been recognized, there has never been previously, so far as is now known, any attempt to regulate or to normalize the redox state in such mammals (including especially human patients) receiving intravenous therapy, in patients undergoing dialysis, or in patients receiving parenteral nutrition. The present invention provides compositions and methods for regulating and/or normalizing the redox state in mammals (including man) treated herewith.

Existing electrolyte fluids make no attempt to maintain or normalize cellular redox potentials in any way whatsoever. In fact, most existing electrolyte fluids actually severely distort or make abnormal the redox balance of the cells, resulting in multiple and definable abnormalities. In this way, existing electrolyte fluids distort, such things as, for example, the rate of fat oxidation, the rate of glucose production, the rate of uric acid excretion, the rate of galactose metabolism in milk fed infants, and the like. All of these abnormalities lead to respectively, accumulation of fat in tissue, such as, for example, liver, production of either hyperglycemia or hypoglycemia, gouty crisis, cataracts, and neurological damage.

B. The phosphorylation Potential

Just as the $[\text{NAD}^+]/[\text{NADH}]$ ratio is defined as a "redox state", by analogy, it is customary to define the energy state of the adenine nucleotide co-enzyme couple

1 as the "phosphorylation potential". Because in living
cells ATP, ADP, and HPO_4 exist in several charged forms,
and in various complexation states with Mg^{2+} , it is
customary to define these forms as sigma ATP, sigma ADP,
5 and sigma Pi. The phosphorylation potential is thus
defined by the relationship $[\text{sigma ATP}]/[\text{sigma ADP}]$
 $[\text{sigma Pi}]$.

It is clear that the reaction of oxidative phos-
phorylation contains both the redox state of mitochondria
10 and the cytoplasmic phosphorylation potential. While
the phosphorylation potential cannot apparently be con-
trolled directly by addition of ATP and ADP to fluids
contacting cells, since these compounds do not penetrate
cell wall, there is, however, another reaction which is
15 in near-equilibrium with the cytoplasmic $[\text{sigma ATP}]/$
 $[\text{sigma ADP}][\text{sigma Pi}]$ (see Veech et al. in J. Biol. Chem.
254, 6538-6547, 1979). The reaction involves the two
most active enzymes in the glycolytic sequence found in
nearly all living cells and catalyzed by the enzymes
20 glyceraldehyde 3-phosphate kinase (EC 2.7.2.3).
Veech et al. (reference just cited) provide an equation
which defines the relationship between the free cytoplasmic
 $[\text{NAD}^+]/[\text{NADH}]$ or redox state and the cytoplasmic phosphy-
lation state or $[\text{sigma ATP}]/[\text{sigma ADP}][\text{sigma Pi}]$. This
25 relationship is now and accepted by those familiar
with this art and is (equation 5):

$$K_{G+G} = \frac{[\text{sigma 3-PG}][\text{sigma ATP}]}{[\text{sigma GAP}][\text{sigma ADP}][\text{sigma Pi}]} \cdot \frac{[\text{NADH}][\text{H}^+]}{[\text{NAD}^+]} = 1.83 \times 10^{-4}$$

or

$$30 \quad \frac{K_{G+G}}{K_{LDH}} = \frac{[\text{sigma 3-PG}]}{[\text{sigma DHAP}]/22} \cdot \frac{[\text{sigma ATP}]}{[\text{sigma ADP}][\text{sigma Pi}]} \cdot \frac{[1\text{-lactate}]}{[\text{pyruvate}]} =$$

$$1.65 \times 10^{+7} \text{M}^{-1}$$

35

1 metabolism in any living cell may be considered to
be an ordered process whereby $[H^+]$ and electrons $[e^-]$
are removed from substrates and passed to co-enzyme ac-
ceptors which are largely cytoplasmic NAD^+ . This co-
5 factor thus has a potential in the cell for more oxidation
at about -0.19 volts than its standard potential of about
-0.32 volts so that it may accept these electrons.
The H^+ and e^- gathered in the cytoplasm, or even created
in the mitochondria, may then be transferred to mitochon-
10 dria by mechanisms involving other substrates to mito-
chondrial NADH which has a lower potential of about -0.28
volts in most mammalian cells. If e^- and H^+ are produced
with a higher voltage, such as for example, from the oxi-
dation of succinate or fatty acids, they form reduced
15 FADH₂ from FAD which has a more oxidized potential and
therefore less potential energy. H^+ and electrons
produced from NADH-linked substrates produce 3 ATP for
each $1/2 O_2$ consumed while those from flavo-protein
(FAD) acceptors produce only 2. This difference in energy
20 is due to the fundamental difference in the chemical
reactions involved in producing the H^+ and e^- .

The fundamental process of cell respiration where
NADH is oxidized to form heat and energy is called
oxidative phosphorylation. It occurs in cellular organel-
25 les called mitochondria in a series of redox reactions
called the electron transport chain. The mitochondrial
electron transport system takes two electrons $[2e^-]$
from substrates and passes them up the chain to reduce
 $1/2 O_2$ forming H_2O . The energy realized in this process
30 is conserved in the cell in a chemical form of anhydride
bond in the terminal phosphate group of adenosine tri-
phosphate (ATP). The formation of three pyrophosphate
bonds of ATP leads to the formation of H_2O and requires
 $3H^+$ in addition to the formation of the 1 H_2O formed from
35 NADH plus H^+ plus $2 e^-$ taken from the substrates being
oxidized by the cell. The reaction of oxidative

1 phosphorylation is a spontaneous one (see Veech et al
in cited reference).

The phosphorylation potential of living cells can
be measured by determining the cellular contents of the
5 components of certain metabolites (see Veech R.L., In
J. Biol. Chem. 254, 6538-6547, 1979). In certain tissues,
such as brain, heart, or skeletal muscle, measurement of
the components of the creatine kinase reaction (EC 2.7.3.2)
may be used as the preceding reference describes.

10 Since on theoretical grounds Veech et al. in
J. Biol. Chem. 254, 6538-6547, 1979 showed that $[\text{creatine}]/$
 $[\text{creatine-P}]$ is in near equilibrium with the cytoplasmic
 $[\sigma \text{ ATP}]/[\sigma \text{ ADP}]$, it follows that the phosphor-
ylation potential in skeletal muscle or brain may be
15 evaluated in living human patients by measuring the
 $[\sigma \text{ CRP}]/[\sigma \text{ Pi}]$ ratio without resorting to freeze-
clamping of organs by the use of ^{31}P NMR (nuclear-mag-
netic resonance) as has been done by Chance and others
(see Chance B., et al., Proc. Nat'l. Acad. Sci., U.S. 78
20 6714-6718, 1981). The agreement between the necessarily
destructive methods heretofore used in animals by Veech,
and the somewhat less precise but nonharmful methods of
 $\sigma \text{ creatine-P}/\sigma \text{ Pi}$ measurements with ^{31}P NMR,
demonstrate that the normal value of the phosphorylation
25 potential or $[\sigma \text{ ATP}]/[\sigma \text{ ADP}][\sigma \text{ Pi}]$ as esti-
mated by Veech is essentially correct (as stated above).
Further, the increasing availability of ^{31}P NMR facilities
in academic medical centers ensures that measurements in
living human patients can be conducted without harming
30 them.

Because the cytoplasmic $[\sigma \text{ ATP}]/[\sigma \text{ ADP}]$
 $[\sigma \text{ Pi}]$ or phosphorylation potential is related to the
cytoplasmic $[\text{NAD}^+]/[\text{NADH}]$ or redox state by a near-
equilibrium reaction catalyzed by glyceraldehyde-3-
35 phosphate dehydrogenase and 3-phosphoglycerate kinase,

SUBSTITUTE SHEET

1 it is possible to alter and regulate and normalize
the phosphorylation potential of a living cell by affect-
ing its redox state (as is believed to be accomplished in
the present invention).

5 If a simple, reliable chemical means were known
and/or could be devised to change the intracellular redox
state, it would of necessity have to change the other
components of the reaction which include the phosphory-
lation potential and would be of obvious fundamental
10 importance in medicine and in many other related fields
of biochemistry, physiology, molecular biology,
tissue culture, veterinary medicine, and like endeavors.
Such a chemical means is provided by the teachings of
the present invention.

15 C. Redox Active Metabolites

As above indicated, a large portion of metabolism
is devoted to energy generation which involves the re-
moval of H^+ and e^- from substrates in cytoplasm or mito=
chondria for delivery to mitochondrial electron transport
20 scheme for conversion of $2H^+$ plus $2e^-$ with $1/2 O_2$ to
yield H_2O with the liberation of about 1 volt or 54
kcal/mole of energy which is conserved in the [sigma
ATP]/[sigma ADP][sigma Pi]couple. In mammalian cells,
the [sigmaATP]/[sigma ADP][sigmaPi]has a delta G(free
25 energy in kilocalories per mole) of between -13.6 and
014.1 Kcal/mole, the transfer to this H^+ and e^- is
accomplished by a series of co-factors, the major one
being NAD (nicotinamide adenine dinucleotide) and its
phosphate (called NADP). Oxidation is defined as the
30 removal of electrons, and reduction as the addition of
electrons. The removal or addition of e^- plus H^+
from substrates is catalyzed by enzymes, the major group
of which are called dehydrogenases, as indicated above.
The enzymes (catalysts) control the rates at which reac-
35 tions occur, but the extent and the direction of a

SUBSTITUTE SHEET

1 reaction, and the amount of energy (ΔG) which may
be liberated by a reaction, is determined by the inherent
energy in the chemical bonds (ΔG^0) and the concentra-
tions of the reactants and products.

5 Determination of any redox or energy state must
always involve a ratio of chemical compounds, [oxidized
product]/ [reduced reactant] and [oxidized co-factor]/
[reduced co-factor]. The overall reaction is thus com-
prised of two individual redox systems, one of which is
10 oxidized, while the other is reduced.

Those enzymes within a cell which are of suffi-
ciently high activity relative to the flux through the
enzyme to catalyze a state of near equilibrium are suitable
for controlling the redox state. A reaction may be ex-
15 perimentally determined to be in a state of near-
equilibrium by measuring the equilibrium constant (K_{eq})
under conditions which approximate those existing within
a cell, that is, where the ionic strength I equals 0.25,
the pH equals 7 to 7.2, the temperature equals 38°C,
20 and the free $[Mg^{2+}]$ equals 0.5 to 1mM, and also where I
equals $1/2$ sigma molarity of ions times the valence of
ions. With knowledge of the value of K_{eq} , the concentra-
tion of the reactants in a tissue may be measured in
rapidly frozen tissue. If the value of [product]/
25 [reactant] measured, in several different dehydrogenase
reactions, gives the same calculated free $[NAD(P)^+]$ /
[NAD(P)H] ratio, then the reaction is said to be in
"near-equilibrium" under in vivo conditions. In the case
of near-equilibrium dehydrogenase reactions, addition of
30 a predetermined amount of a ratio of product/reactant
allows one to set the $[NAD^+]/[NADH]$ ratio within the cell
at a predetermined level, provided the reactants penetrate
the cell wall freely or in a constant ratio one to another
The redox state or $[NAD(P)^+]/[NAD(P)H]$ ratio may be set in-
35 side a cell by controlling the $[CO_2]$ and the redox state
of the cytoplasmic free $[NAD^+]/[NADH]$ as described pre-

SUBSTITUTE SHEET

1 virously. Each of the three couples employed in this
invention is a near equilibrium couple.

 Various cytoplasmic and mitochondrial NAD-linked
dehydrogenases appear to be capable of controlling or
5 setting the $[NAD^+]/[NADH]$ ratio in each of cytoplasm
and mitochondria. Because of the special permeability of
the complete couple of L-lactate⁻/pyruvate⁻ for cytoplasm
and D-B-hydroxybutyrate⁻/acetoacetate for mitochondria,
these two redox couples are preeminently well suited for
10 the practice of this invention. This is so because:
1) both monovalent anions in the pair distribute themselves
equally between plasma and cellular H₂O; 2) changes in
distribution of anions between extracellular and intra-
cellular H₂O during pathological states will effect both
15 members of the couple equally through preserving the inte-
grity of the given redox state; 3) both couples react
with "dead end" branches off the main metabolic sequences;
4) the concentration of these normal transport metabolites
can reach very high levels in plasma of normal healthy
20 mammals under physiological conditions; and 5) the mem-
bers of both couples each contain a charge which can be
used to normalize the low Na⁺:Cl⁻ milliequivalent
ratio characteristic of most I.V. (intravenous)
solutions.

25 The near equilibrium redox active metabolite
carboxylate couples employed in the practice of the
present invention, specifically, L-lactate⁻/pyruvate⁻
and D-B-hydroxybutyrate⁻/acetoacetate⁻, constitute
safe entry points and appear to be unusual in their
30 ability to not only normalize the redox state in cyto-
plasm through the reaction of L-lactate and pyruvate
with LDH, but also to regulate the redox state in the
mitochondria through reaction of D-B-hydroxybutyrate
and acetoacetate with the enzyme D-B-hydroxybutyrate
35 dehydrogenase (EC 1.1.1.30) which is apparently present

SUBSTITUTE SHEET

1 in most tissues at a high enough activity to maintain
near-equilibrium conditions at most times.

 As indicated above (see Table 1 and related
text), previous attempts to normalize the sodium to chlor-
5 ide milliequivalent mole ratio of about 1.36 were usually
done by adding either (d,l) lactate⁻ or acetate⁻, or a
combination of lactate and acetate, or other inappropri-
ately paired carboxylate anions, leading inevitably
in all known instances to severe and measurable patholo-
10 gical consequences.

 In the solutions of the present invention, one
employs at least one of the above indicated three dif-
ferent near-equilibrium couple mixtures. In each couple
mixture, the two member components are employed in a
15 definite milliequivalent ratio relative to one another
Such a ratio is needed in order to control either the
plasma pH, or the redox state (and consequently the
phosphorylation potential), or both.

 Among the possible mixture couples which could be
20 used, these three couples were selected because, for
each couple:

1. The distribution of ions between extra-
cellular fluid and intracellular fluid is
predictable in all normal and pathological
25 states.
2. It is capable of achieving and regulating a
predetermined redox state and phosphorylation
potential within most living cells.
3. At least one member thereof contains an
30 anionic charge.
4. It can be given in aqueous solution form so
that the total levels administered do not
substantially exceed total levels found under
normal physiologic conditions in mammalian
35 blood (plasma).

SUBSTITUTE SHEET

- 1 5. Both members thereof constitute safe entry
points which enter the metabolic sequence and
pathways at a safe entry point and these safe
entry points, are at dead end terminals in the
5 metabolic pathways, thus avoiding any
possibility of a pathologic buildup of
metabolites with the consequence that a
disordering of cellular metabolism would
consequently result.
- 10 6. It need not induce a change in water distri-
bution between intracellular and extracellular
space.
7. It may be osmotically neutral in most tissues.
8. Administration permits control of water distri-
15 bution as a result of changing redox and
hence the linked phosphorylation state and
the magnitude of the extracellular Na^+
Donnan forces generated thereby.

 When blood levels of, respectively, l-lactate/
20 pyruvate, d-betahydroxybutyrate/acetoacetate, and bicar-
bonate/ CO_2 are maintained within their normal limits,
then the redox state, the phosphorylation state, and the
plasma pH each tend to be normalized which is achieved
as a result of administration of a solution of this
25 invention.

 Intracellular concentration of each member of each
couple is achieved through the extracellular fluid because
each of the monovalent anions chosen, namely, l-lactate
and pyruvate, d-betahydroxybutyrate, and acetate,
30 and also bicarbonate, distribute themselves between
plasma water, extracellular water, and intracellular
water in concentration ratios or gradients which are the
inverse of the hydrogen ion (concentration), thereby
achieving a gradient or ratio of about 1.35 between
35 extracellular and intracellular fluid. The nonionic

SUBSTITUTE SHEET

- 1 dissolved CO_2 distributes itself substantially equally
between extracellular fluid and intracellular fluid.

Those learned in the art realize a redox state must
be defined at a certain pH, or $[\text{H}^+]$ ion concentration.

- 5 The near-equilibrium couple $[\text{HCO}_3^-]/[\text{CO}_2]$ defines the cel-
lular pH or $[\text{H}^+]$ concentration. This near-
equilibrium couple is therefore an integral part of the
redox state. Preferably the level of sigma $[\text{HCO}_3^-]$
plus $[\text{CO}_2]$ present in any given solution of this invention
10 may vary under normal physiological conditions from about
10mM/l to 40mM/l, but in general, is (when present) in
the range from about 25 to 35 mM/l. The milliequivalent
ratio of $[\text{HCO}_3^-]/[\text{CO}_2]$, of course, in effect, is defined
so as to give a $[\text{H}^+]$ ion concentration, or pH, in the
15 physiological range as defined above.

- The redox and phosphorylation states in various
tissues in the rat have been given by Veech et al. J.
Biol. Chem. 254, 6538-6547, 1979 and for the redox states
in Veech, Eggleston and Krebs, Biochem. J. 115, 609-
20 619, 1969. The same general principles are believed to
hold for man, but cannot be directly proved since freeze
clamping is not possible. MNR measured estimates of the
phosphorylation potential in brain and muscle in living
humans, however, agree well with these figures derived
25 by freeze clamping procedures.

- By the term "plasma" or "blood plasma" as used
herein conventional general reference is had to the liquid
part of the blood as distinguished from the corpuscles.
Plasma can be prepared by various techniques well known
30 to those familiar with this art typically using centri-
fugal force to separate a supernatant (which is plasma)
after non-coagulated blood is centrifuged.

1 By the term "extracellular fluid" as used herein
conventional general reference is had to all body fluids
in extracellular spaces outside of the circulatory system
(e.g. the blood) and outside of intracellular fluid in
5 a mammal (typically constituting about 15% of the weight
of a mammal).

By the term "intracellular fluid" as used herein
conventional general reference is had the fluid within
cells which constitutes about 57% of total mammalian
10 body weight.

It is well known that (see Black DAK. Lancet i
305-12 1953) infusions into a mammal of large amounts
sodium and chloride in a solution milliequivalent ratio
of 1 to 1 lead inherently to hyperchloremic acidosis.
15 This knowledge lead to the development of such well known
solutions as lactated Ringers, and also to the composi-
tions used in most dialysis solutions, wherein, in a
majority of cases, the sodium to chloride milli-
equivalent ratio is normalized compared to plasma values
20 by the addition of various organic anions (as described
above). These organic anions chosen in the prior art
are as described above. In no known prior art case,
however, were any solutions with a normalized Na:Cl
milliequivalent ratio produced which did not use organic
25 ions in such a way as to inherently lead to severe and
measurable metabolic abnormalities and pathologic
consequences. Mixtures of redox pairs nor $\text{HCO}_3^-/\text{CO}_2$
were not generally used to normalize the $\text{Na}^+:\text{Cl}^-$ ratio
nor were the reasons known why a choice of near equili-
30 brium matched couples was desirable. Correction of this
ratio between sodium cation and chloride anion by the
mixture couples as taught by the present invention
eliminates the pathologic consequences of all the
prior art electrolyte solution compositions. In addi-
35 tion, the solution compositions of this invention tend

SUBSTITUTE SHEET

1 to normalize plasma inorganic electrolyte composition and
to correct the anion gap which in many instances could
not be accomplished by prior art electrolyte solutions.

Thus, in summary, the compositions of this inven-
5 tion tend to normalize (a) plasma pH, (b) composition of
major plasma inorganic electrolytes, (including the
milliequivalent ratio of Na^+Cl^- and the anion gap),
(c) the redox state, and (d) the phosphorylation poten-
tial. These normalizations are obtained and achieved
10 without the abnormal, pathological consequences
inherent in all known prior art solutions. No other
man-made solutions are presently known which will ac-
complish this combination of results.

D. Other Possible Benefits (Theorized).

15 It is theorized, and there is no intent to be
bound by theory herein, that the solutions of the
present invention, in addition to the properties above
described, further tend to normalize at least one
of the following states:

- 20 1. Distribution of water between intracellular
and extracellular compartments,
2. Distribution of major inorganic electrolytes
between intracellular and extracellular fluid,
3. Transmembrane cellular potential, and
- 25 4. The degree of organization within the living
cell or its entropy.

The ratio of the chemical activity of free water
on each side of a typical normal mammalian cell membrane
is always unity. Movement of water across such a cell
30 membrane is achieved by the movement of osmotically
active substances. Changing the cellular phosphorylation
potential, through the NaK ATPase, therefore,

1 Transmembrane cellular potential can be measured
by known (e.g. conventional) techniques: such as with
electrodes or probes, and the like. Calculation of such
cellular voltage can be achieved from a measurement of
5 the distribution of chloride ions between intracellular
and extracellular fluid following Nernst's law.

A quantitative relationship is theorized to exist
involving redox state, phosphorylation potential and
the above referenced three states. This relationship
10 may be expressed by the following equation:
(7.)

$$\begin{aligned} \Delta G = 0 = & \Delta G^{\circ}_{\text{ATPase}} + \Delta G^{\circ} \frac{[\text{Na}^+]}{[\text{Na}^+]} \dots + RT \ln \frac{[\Sigma \text{ADP}][\Sigma \text{P}_i]}{[\Sigma \text{ATP}]} \\ 15 & + RT \ln \frac{[\text{Na}^+]_o^3 [\text{K}^+]_i^2 [\text{Cl}^-]_o}{[\text{Na}^+]_i^3 [\text{K}^+]_o^2 [\text{Cl}^-]_i} + T \Delta S \end{aligned}$$

wherein

The values of the various terms in the foregoing
equation of are given as follows (for muscle and brain):
20 (7.)

$$\begin{aligned} \Delta G = 0 = & -7.73 \text{ kcal/mol} + 0 = (-6.3 \text{ kcal/mol}) \\ & + 8.4 \text{ kcal/mol} + 5.6 \text{ kcal/mol} \end{aligned}$$

In the foregoing equation, the phosphorylation
25 potential is shown to be in a state of near equilibrium
with the substrates of the sodium potassium ATPase.
Since the chloride ion is cell wall permeable, this ion
distributes itself in conformity with the transmembrane
cellular potential. Movement of three sodium ions out
30 of the cell and two potassium ions into the cell across
the cell membrane necessarily results, from the law of
electrical neutrality, in the movement of one chloride
ion from inside the cell to outside the cell across
the cell membrane. This makes the sodium potassium
35 ATPase, in effect, an osmopump resulting in the export

SUBSTITUTE SHEET

1 of two milliosmoles per ATP hydrolyzed. This pump
is electro-neutral.

5 The T delta S term, which is approximately
5.6 kilocalories per mole of ATP hydrolyzed, is an
entropy term. It, therefore, refers the state of
randomness within the cell. The positive nature of this
entropy term indicates that a high degree of order is
10 imposed on the intracellular environment. In terms of
quantum and statistical mechanics, the number of ways
of achieving a certain energy state is called its de-
generacy (Ω). The Boltzmann equation defines S (or
entropy) as $S = K_B \ln \Omega$, where Boltzmann's constant
(which relates the gas constant to Avogadro's number),
or $K_B = 1.38 \times 10^{-23} \text{ J/}^\circ\text{K}$.

15 It follows from the foregoing equation 7, above,
that the distribution of calcium inside the cell is a
function of the cube of the respective sodium concentra-
tions inside and outside of the cell because of the action
of the high-activity sodium-calcium exchange enzyme.

20 The following equation shows the relationship:

$$K_{\text{Na/Ca}} = \frac{[\text{Na}^+]_i^3 [\text{Ca}^{2+}]_o [\text{Cl}^-]_i}{[\text{Na}^+]_o^3 [\text{Ca}^{2+}]_i [\text{Cl}^-]_o}$$

where:

25 $[]_i$ ~ intracellular concentration in cytoplasmic H_2O
 $[]_o$ ~ concentration in extracellular H_2O .

Unlike the simple NaK ATPase which moves 2
mOsmoles out of the cell thus moving H_2O with it, the
result of moving Ca^{2+} out of the cell by the Na-Ca
30 exchanger is to move a net of 3 mOsmoles into the cell,
thus increasing the cells water content. The NaK
ATPase must then operate again to move the excess
sodium out in exchange for K^+ to restore osmotic
equilibrium between extracellular space H_2O and cell
35 H_2O .

SUBSTITUTE SHEET

1 The net result of the foregoing equation (7)
 is that the water of both intracellular and extracel-
 lular fluid is a function of the sodium/potassium ATPase
 (EC 3.6.1.3) and also of the phosphorylation
 5 potential.

It can be empirically seen that the voltage
 across a cell membrane is inversely related to the
 chloride distribution and the phosphorylation
 potential.

10 Correlation between phosphorylation potential,
 intracellular chloride and transmembrane cellular
 potential for various mammalian tissues is illustrated
 by Table II below:

Table IIa

15 Correlation between Phosphorylation Potential,
 Intracellular Chloride and Transmembrane Cellular
 Potential.

	$\frac{[\sum \text{ATP}]}{[\sum \text{ADP}][\sum \text{Pi}]}$ M^{-1}	$[\text{Cl}^-]_i$ mEq/l	ΔE mV
20 red cell	7,000	90	- 9
liver	15,000	40	-40
brain or muscle	30,000	7-9	-70

From Table II, it is seen that low phosphorylation
 25 potential correlates with a high intracellular chloride,
 and a low transmembrane cellular potential correlates
 with the inherent setting of the potential as a function
 of the Donnan-active material within the cell with the
 phosphorylation potential merely overcoming the Donnan
 30 forces so as to export two milliosmoles, as described
 in equation 7.

Because of the voltage dependent permeant
 nature of chloride ion to most non-epithelial tissues
 (Ho, MK, Guidotti G. J. Biol Chem 250: 675-683, 1975)
 35 the induction of high extra cellular chloride, such

SUBSTITUTE SHEET

1 as occurs, for example, in current intravenous electro-
 lyte therapy, must have profound pathological conse-
 quences for the metabolism of the cell, even though the
 purpose of such intravenous and dialysis therapy is to
 5 normalize the water and electrolyte concentrations of
 the various mammalian body cellular compartments.

This is so because the ratio

$$\frac{[\text{Na}^+]_o^3 [\text{K}^+]_i^2 [\text{Cl}^-]_o}{[\text{Na}^+]_i^3 [\text{K}^+]_o^2 [\text{Cl}^-]_i}$$

10 and the $T\Delta S$ term link the cellular phosphorylation and
 the cellular redox states to intracellular and extra-
 cellular water and the electrolyte concentrations of
 Na^+ , K^+ , Cl^- and also Ca^{2+} .

15 E. Electrolyte Solution Preparation

The electrolyte solutions of the present invention
 can be prepared by any convenient or conventional pro-
 cedure.

As a matter of accuracy, the compositions of
 this invention can be described in terms of their ion
 20 contents which can be expressed either in terms of milli-
 moles per liter of solution, or milliequivalents per
 liter of solution. It is standard practice in this art
 in describing a given solution to separate anions from
 cations, and nonionics from ionic materials; this
 25 practice is followed herein in the main. As those skilled
 in the art will readily appreciate, a translation or
 conversion of millimoles per liter of solution, or of
 milliequivalents per liter of solution, into grams of
 a given salt added per liter of water is routine and
 30 is given in any standard text book in the field, such
 as, for example, "Data For Biochemical Research"
 (1969) (Dawson R.M.C., Elliott W.H., Jones K.M., Eds).
 Clarendon Press, Oxford at pages 507 and 508. This
 reference illustrates not only the salt starting
 35 materials, but also the order of addition of same

SUBSTITUTE SHEET

1 in the preparation of certain illustrative prior art
electrolyte solutions shown therein. Solutions of this
invention are readily prepared by this type of procedure.
The particular salt combination used for a given solution
5 may change from time to time in a manufacturing operation
as those skilled in the art well know. The significant
factor is that the final concentrations of respective
component ions in any given solution remain as speci-
fied or desired. In view of the developed state of this
10 art, no detailed description of electrolyte solution
preparation procedures is believed to be necessary or
desirable herein.

The solutions of this invention, and the component
materials incorporated therein, are, in general,
15 formulated, so as to contain a combination of a the
desired physiological $\text{Na}^+:\text{Cl}^-$ milliequivalent ratio
normality, one or more of these three near-equilibrium
couple(s), and other components.

Thus, various initially existing pathological
20 conditions can be ameliorated by practice of the processes
and the compositions of the present invention, depending
upon the particular solution used and the particular
use conditions and circumstances in any given use situa-
tion. Thus, by this practice of this invention, one
25 can accomplish in a physiologically acceptable manner
the removal of metabolic products from cellular water,
the replacement of body fluids and electrolytes, and
the administration of nutrients, and the like, as desired.
The solutions may be administered in any fashion desired
30 so long as they contact living mammalian tissue.
Administration can be accomplished by any convenient
technique, such as for examples, intravenously, intra-
arterially, intradermally, intrathecally, orally
(especially when the solution contains the non-
35 bicarbonate containing couples),

SUBSTITUTE SHEET

41

1 across a semi-permeable membrane, or the like, as those
skilled in the art will readily appreciate. The solu-
tions of this invention as prepared are, in general,
well suited for the administration of therapeutic agents
5 to living mammals.

When bicarbonate anions are not present, then the
level of combined (or sigma) l-lactate/pyruvate and/or
d-betahydroxybutyrate/acetoacetate present in a solution
of this invention is optionally greater than when bi-
10 carbonate is present in order to achieve the desired
milliequivalent ratio of sodium to chloride, as indi-
cated. The concentration of either sigma l-lactate/
pyruvate and/or of d-betahydroxybutyrate/acetoacetate
in a given solution of this invention can thus range up
15 to the full maximum quantity desired (within the limits
described herein). It is presently preferred, particu-
larly when no bicarbonate is present, to employ a
mixture of l-lactate/pyruvate with a mixture of d-
betahydroxybutyrate/acetoacetate.

20 Those skilled in the art will realize that in
any given solution of this invention one can incorporate
an excess of one or more individual members of any one
mixture couple of this invention so that (a) the ratio
of one member to the other of any given couple and (b)
25 the total quantity of both mixtures or members lies
outside of the ranges hereinabove described without
departing from the spirit or scope of the invention.
Such a single member excess is not recommended when
practicing the present invention. However, if such a
30 single member excess does occur, the amount of the
excess can be calculated by determining the maximum
ratio of one couple member to the other which can
be present in accord with the above teachings, and then
the quantity of one couple member remaining (or present)
35 which is outside of this ratio range may be considered
to constitute an excess. The effect of such an excess

SUBSTITUTE SHEET

1 is evidently merely to cut down, but not to eliminate,
the efficacy of what effect would otherwise be obtained
by using only a solution which contains mole ratios and
quantities of respective mixture couples within the
5 spirit and scope teachings of this invention.

In the making of solutions of this invention,
it is preferred to employ the optically active l-lactate
salts or l-lactic acid (which will make the desired l-
lactate anions in solution), and also similarly to employ
10 d-betahydroxybutyric acid or d-betahydroxybutyrate salts
(which will make the desired d-betahydroxybutyrate anions
in solution). Choice of particular salt or acid (or
mixture) used in any given case depends among various
factors, such as upon the other starting inorganic salts
15 which a formulator desires to use (based upon avail-
ability, cost, and like factors), all as will be readily
appreciated by those skilled in the art. Racemic (d-l)
mixtures could be used, but their use is preferably
avoided since these unnatural isomers are known to be
20 associated with specific toxic effects. Racemates can
be metabolized. If such are used, the ratios of one
member to another in the respective near equilibrium
couples involved should be based upon the quantity of
particular optically active form present (e.g. either
25 [l-lactate⁻] or [d-betahydroxybutyrate⁻], as the case
may be.

In the solutions of this invention at the pH
ranges described, not all couple member material of any
given couple will be in an ionized (anionic or disso-
30 ciated) form; a portion of this material will be in an
un-ionized (undissociated) form. Typically, the quantity
of undissociated material (such as l-lactate acid,
pyruvic acid, d-betahydroxybutyric acid, acetoacetic,
sodium bicarbonate, carbonic acid, or the like) is
35 not more than about 0.1% of the total quantity of all

SUBSTITUTE SHEET

1 material of any given species (e.g. l-lactate, pyruvate,
d-betahydroxybutyrate, acetoacetate, or bicarbonate).
For purposes of calculating a milliequivalent ratio,
molar concentration, or the like, it is preferred to
5 base computations upon the total material of any given
species which is present in a solution of this
invention.

The carbon dioxide, when used, can be intro-
duced either as a gas, preferably using conventional
10 aeration apparatus to effect a solubilization of CO₂
in a solution, or it can be generated in situ from a
dissolved metal (such as sodium(preferred), potassium,
calcium or magnesium) salt of bicarbonate in combination
with a dissolved acid (lactic, pyruvic, betahydroxy-
15 butyric, or acetoacetic) in respective proportions of
each such that the total quantity of dissolved carbon
dioxide so generated is within the ranges described
herein for use in a solution of this invention.

As elsewhere indicated herein, if desired, a
20 solution of this invention can also contain various known
additives in concentrations taught by this art, but it
is presently preferred not to employ anions and non-
ionics which will not be safe entry points.

In general, a solution of this invention should
25 contain as a minimum a total of sigma (lactate/pyruvate
and/or sigma betahydroxybutyrate/acetoacetate) and/or
sigma bicarbonate/carbon dioxide which is at least
about 0.5 millimoles per liter as indicated. Below
these levels, benefits in normalization of body
30 metabolism as explained above are apparently achievable,
but such benefits become increasingly difficult to
demonstrate and prove by state of the art techniques of
measurement. Consequently, it is preferred to avoid,
if possible, homeopathic possibilities by using minimum
35 concentrations as above indicated.

SUBSTITUTE SHEET

1 When bicarbonate is present, the total quantity
of sigma (lactate/pyruvate and/or betahydroxybutyrate/
acetoacetate) used can generally be reduced which is
now believed to be desirable. Thus, when bicarbonate
5 is present, the total sigma (l-lactate/pyruvate and/or
d-betahydroxybutyrate/acetoacetate) is preferably about
2 to 17 millimoles per liter.

 When a solution of this invention contains
at least one osmotically active substance (preferably
10 metabolizable and nonionic), it is added to provide
nutritional or osmotic requirements. Since it is
uncharged, it does not therefore contribute to normaliz-
ing the $\text{Na}^+:\text{Cl}^-$ ratio or to correcting the anion gap.

F. Classification and Usage of Electrolyte Solutions

15 All of the formulations of this invention
from a composition viewpoint fall into what can be
regarded generally as being either one of two distinct
classes:

20 Class I which comprises fluids containing
at least one and not more than two metallic
cations selected from the group consisting
of sodium, potassium, calcium and magnesium,
while

25 Class II which comprises solutions
containing at least three and typically
not more than four metallic cations
selected from the same group.

30 Class I fluids are typically administered at
dose levels which are not greater than about 1 liter
per human adult patient per 24 hour day, one typical
dose level being 500 ml per such patient per 24
hour day.

35 Class II fluids are typically administered at
dose levels chosen by the physician, and these levels
can range from 0 to greater thn 100 liters per human

SUBSTITUTE SHEET

1 adult patient per 24 hour day, depending upon
circumstances.

Each of the inorganic electrolytes present in
a solution of this invention is typically present in
5 an amount of at least about 0.5 mM/l thus clearly quali-
fying them as "electrolytes" as such rather than as
trace metals, such as is associated with levels of
iron, manganese, zinc and the like in normal plasma
and which trace metals can be present in normal plasma
10 at levels less than about 0.4 mM/l. If desired, of
course, trace materials can be added to solutions of
this invention.

Each of the cations sodium, potassium, calcium,
and magnesium and each of the anions bicarbonate, chlor-
15 ide, and phosphate are normally found in the plasma
and tissue of mammals at concentration levels greater
than or equal to about 1 millimolar per liter of body
fluid (see Table I). The solutions of this invention,
in general, contain respective inorganic electrolyte
20 concentrations which resemble the corresponding concen-
trations of such electrolytes in plasma (when any one
of such electrolytes is present in any given solution
of this invention).

Class I solutions are useful as intravenous solu-
25 tions for electrolyte and fluid therapy especially where
no more than about 10% of total blood volume (about
500 ml in an adult human) is to be administered over
a 24 hour day. Solutions of this type have been used
in the treatment of hemorrhagic shock where 2400
30 mOsmolar NaCl solutions have been advocated. (See
Velosco IT, Pontieri V, Rocha M, Silva E,
Lopes OU. Am J Physiol 239: H664-673, 1980).

Class II solutions find use in intra-
venous applications where over 10% of total blood
35 volume (about 500 ml in an adult human) is needed to

SUBSTITUTE SHEET

46

1 to be given to a human adult over a 24 hour day.
Administration can be made, for example, to a normal
human with an impairment or injury, such as loss of
limb or the like, or to a human with impaired renal
5 excretion: Class II solutions can be used as an
improvement for lactated Ringer's solution.

Class II solutions also are useful in dialysis,
peritoneal, ambulatory peritoneal dialysis or hemo-
dialysis, where perhaps 120-160 liters per hemodialysis
10 day per patient are used. Such solutions can be used
improve existing acetate or lactate containing solu-
tions, but use of acetate is not desired in the prac-
tice of this invention.

Given the solutions of this invention, a physician
15 may henceforth wish to administer normal or hypertonic
saline solution only to correct a condition of metabolic
alkalosis since giving $\text{Na}^+:\text{Cl}^-$ in a 1:1 milliequivalent
ratio causes acidosis and other disturbances recognized
herein. The solutions described herein improve normal
20 saline solution.

Solutions of Class II can be used as such, or
can be employed as diluent for plasma extenders or for
reconstituted frozen blood. For example, dehydrated
plasma can be dissolved and dispersed in a solution of
25 Class II so as to produce an injectable solution, as
those familiar with the art will appreciate.

Each one of these Class I and II solutions can
be considered to be characteristically comprised of
four subgroups which can be stated briefly as
30 follows:

- A. Solutions containing only inorganic ions
and one or more of our near-equilibrium
couples of organic anions pairs with
which chloride anions are included.

35

SUBSTITUTE SHEET

- 1 B. Solutions containing in addition to such
 inorganic ions and organic ion pairs a
 mixture of bicarbonate and carbon dioxide.
- 5 C. Solutions containing such inorganic ions
 and organic ion pairs plus non ionic mater-
 ials.
- 10 D. Solutions containing in addition to the
 inorganic ionic material both mixtures of
 bicarbonate and carbon dioxide (as
 characterized in B above) plus other
 nonionics (of the type characterized in C
 above).

15 As indicated above, avoidance of substances in
 solutions of this invention which do not constitute safe
 entry points is preferred. For example, use of such
 nonionic osmotically active substances as fructose and
 glycerol are preferably avoided and are not recommended
 for use in the practice of this invention. Also, avoid-
20 ance of the organic anions used in the prior art which
 are not safe entry points is recommended, including use
 of lactate alone, acetate alone, lactate and acetate
 together, gluconate, citrate, and the like.

25 Prior art in dialysis fluids show that the compo-
 sition of the fluids now commercially used evidently is
 intended to approximate that of plasma with the proviso
 that the anion gap is typically corrected with abnormal
 amounts of typically acetate or lactate. The sugges-
 tion has also been made in the prior art dialysis fluid
 composition should approximate the composition of
30 interstitial (extracellular) fluid. While such
 compositional approximations now appear to be
 essentially incorrect especially from the standpoint
 of achieving dialysis fluids of maximal
 safety and utility and patient benefit, it is sub-
35 mitted that such approximations can be substantially

SUBSTITUTE SHEET

1 benefitted by compounding dialysis solutions in accord
with the teachings of the present invention (both for
hemo- and peritoneal dialysis).

5 Solution compositions of the present invention
of Class I and Class II are generically characterized
herein above. The following Table III summarizes
preferred solutions of this invention in terms of compo-
sition at the time of administration (e.g., water
having dissolved therein each of the indicated components
10 in the respective amounts indicated).

With regard to the term "nonionics" in a
solution or process of this invention, those skilled
in the art will appreciate that this term connotes no
net charge on the molecule involved at the particular
15 solution pH specified.

Solutions of this invention can be prepared
as concentrates which at 0.8 molar solutes or greater
will inhibit bacterial growth, as those skilled in the
art will appreciate, and such concentrates can then
20 be diluted with water before administration to prepare
compositions of this invention.

In general, solutions of this invention are
believed to be preparable so as to be storage stable
for periods of time at least sufficient to permit pack-
aging, intermediate storage in sealed containers,
25 followed by administered.

SUBSTITUTE SHEET

Table III
Generic Compositions of Class I and Class II Solutions

5	Component	Composition of time of Administration Quantity Range (millimoles per liter)	
		broad	preferred
	Total cations (mEq/L)	1 to about 2400	130 to 170
	(1) sodium ⁺	1 to about 2400	130 to 165
10	(2) potassium ⁺	0 to about 90	0 to 5
	(3) calcium ⁺⁺	0 to about 60	0 to 1.5
	(4) magnesium ⁺⁺	0 to about 15	0 to 1
	Total anions (mEq/L)	about 1 to 2400	130 to 170
	(5) chloride ⁻	0.6 to about 1940	80 to 130
15	(6) bicarbonate ⁻	0 to about 465	0 to 60
	(7) sigma l-lactate ⁻ / plus pyruvate	0 to about 465	0 to 60
	(8) sigma d-betahydroxy- butyrate/plus acetoacetate ⁻	0 to about 465	0 to 60
20	(9) sigma (6+7+8)	0.1 to about 465	25 to 65
	Total nonionics	0 to about 2400	0 to 305
	(10) carbon dioxide	0 to about 25	1 to 5
	(11) osmotically active substances*	0 to about 2400	0 to 300

In Table III solutions the component interrelationships are always such that the following holds:

30	(12) mEq.ratio of bicarbonate ⁻ / CO ₂	about 0.1/1 to 55/0.1	0.1 to 55/0.1
	(13) mEq.ration of l-lactate / pyruvate	about 20/1 to 1/1	10/1 to 5/1
35	(14) mEq.ratio of d-betahydroxybutyrate ⁻ / acetoacetate	about 6/1 to 0.5/1	3/1 to 1.5/1

SUBSTITUTE SHEET

50

(15) mEq.ratio of Na:Cl	about 1.24 to 1.60	1.24 to 1.6
(16) Osmolarity of Solution	about 260 to 5000	280 to 545
(17) pH of Solutions	about 5 to 9	5 to 9
5 * Glucose preferred		

SUBSTITUTE SHEET

Optionally, solutions of this invention as shown in Table III can additionally contain:

- (a) from 0 to about 25 millimoles per liter of sigma inorganic phosphate (e.g. all inorganic phosphate, including mono-, di-, and tri-valent phosphate ions), and
- (b) from 0 to about 2 millimoles per liter of sigma inorganic sulfate (e.g. all inorganic sulfate including non ionized dissolved salts).

The electrolyte solutions of such Table III, as indicated above, are useful in such applications as intravenous administration for replacement of electrolytes and fluids, for parenteral nutrition, for dialysis, and the like. For a particular field of use and/or end use applications, the formulation of any given solution can be optimized in accord with the desires of the formulator. Thus, in general, the present invention provides one aspect an in vivo process which

- (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions,
- (b) tends to maintain normal plasma and cellular pH, and
- (c) tends to maintain normal cellular cofactor ratios (that is, tends to maintain and regulate a normal cellular redox state and a normal cellular phosphorylation potential).

This process is practiced by introducing into a living mammal a physiologically effective amount of an aqueous solution as above characterized. Introducing can be accomplished by any known procedure as herein indicated. The physiologically effective amounts are as herein indicated.

Class I solutions which are particularly suited for electrolyte and fluid therapy are subgenerically characterized in Table IV below. Each Table IV solution

SUBSTITUTE SHEET

comprises water which has dissolved therein each of the indicated components in the respective amount indicated. In this Table IV the "preferred" class of embodiments (so identified) can be regarded as being usable either
5 as such, or as concentrates which can be further diluted so long as nonionic material is included to keep the final osmolarity above about 260/mOsmoles/L. In the latter case, the diluted solutions should contain added dissolved nonionic material (preferably glucose) with
10 care being taken to preserve in the product diluted solution the various ratios, osmolarity and pH values, all as shown in such Table IV.

Such Class I solutions are used, in accord with this invention, in an in vivo process for accomplishing
15 electrolyte and fluid therapy in a mammal. This process:

- (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions,
- (b) tends to maintain normal plasma and
20 cellular pH, and
- (c) tends to maintain normal cellular cofactor ratios.

This process comprises introducing intravenously into a mammal at a physiologically effective rate a
25 quantity of such a solution in an amount which is not more than about 1 liter per 70 kilograms of mammal body weight per 24 hour day.

SUBSTITUTE SHEET

53

Table IV

Class I Solutions Particularly Suited for Electrolyte and Fluid Therapy

5	Component	Composition at time of Administration	
		Quantity Range	
		(millimoles per liter)	
		broad	preferred
	Total cations (mEq/L)	1 to about 2400	130 to 170
10	(1) sodium ⁺	1 to about 2400	130 to 165
	(2) potassium ⁺	0 to about 90	0 to 10
	(3) calcium ⁺⁺	0 to about 60	0 to 5
	(4) magnesium ⁺⁺	0 to about 15	0 to 3
	Total anions (mEq/L)	1 to about 2400	130 to 170
15	(5) chloride ⁻	0.6 to about 1935	80 to 130
	(6) bicarbonate ⁻	0 to about 465	0 to 60
	(7) sigma l-lactate/ plus pyruvate	0 to about 465	0 to 60
20	(8) sigma d-betahydroxy- butyrate plus acetoacetate	0 to about 465	0 to 60
	(9) sigma (6+7+8)	0.4 to about 465	25 to 60
	Total nonionics	0 to about 2400	0 to 300
	(10) carbon dioxide	0 to about 25	0 to 5
25	(11) osmotically active substances*	0 to about 2400	0 to 300

In Table IV solutions, the component interrelationships are always such that:

30	(12) mEq.ratio of HCO ₃ CO ₂ about 0.1/1 to 55/0.1	12/1 to 85/1
35	(13) mEq.ratio of l-lactate / pyruvate	about 20/1 to 1/1 10/1 to 5/1

SUBSTITUTE SHEET

54

- | | | | |
|---|------------------------------------|--------------------|--------------|
| | (14) mEq. ratio of d- | | |
| | betahydroxybutyrate ⁻ / | | |
| | acetoacetate | about 6/1 to 0.5/1 | 3/1 to 1.5/1 |
| | (15) mEq. ratio of Na:CL | about 1.24 to 1.6 | 1.26 to 1.6 |
| 5 | (16) Milliosmolarity of | | |
| | Solution | about 260 to 5000 | 260 to 540 |
| | (17) pH of solution | about 5 to 9 | 7 to 8 |
| | *glucose preferred | | |

SUBSTITUTE SHEET

Class II solutions which are particularly suited for electrolyte and fluid therapy are sub-generically characterized in Table V below. As before, each Table V solution comprises water which has dissolved therein the indicated components in the respective amount indicated. In this Table V, the "preferred" class of embodiments (so identified) can be regarded as being representative of compositions which are now believed to be suitable for usage, for example, by hospitals and the like. In making and using all these solutions, care should be taken to preserve the various ratios, osmolarity, and pH values, all as shown in such Table V.

Such Class II solutions are used, in accordance with this invention in an in vivo process for accomplishing electrolyte and fluid therapy in a mammal. Parenteral nutrition optionally can be concurrently accomplished (depending upon the content of nutrients, such as nonionic osmotically active substances (like glucose, or other conventional additives, including amino acids). As with the process involving Class I solutions, this process:

(a) tends to maintain the normal plasma milliequivalent ratio of sodium cations to chloride anions, and

(b) tends to maintain normal plasma and cellular pH ratios, and

(c) tends to maintain normal cofactor ratios.

This process comprises intravascularly introducing into the blood of a mammal a physiologically effective amount of such a solution. The quantity introduced can vary per 24 hour day per patient depending upon the circumstances, patient condition, physicians purpose, and the like. No minimum or maximum definite limit on safe usage quantity is now known or believed to exist.

SUBSTITUTE SHEET

Table V

Generic Composition of Class II Solutions for Electrolyte and Fluid Therapy

5	Component	Composition at time of Administration	
		Quantity Range	
		(millimoles per liter)	
		broad	preferred
	Total cations (mEq/L)	1 to about 170	136 to 170
10	(1) sodium ⁺	1 to about 170	130 to 160
	(2) potassium ⁺	0 to about 10	3 to 5
	(3) calcium ⁺⁺	0 to about 5	1 to 1.5
	(4) magnesium ⁺⁺	0 to about 5	0.5 to 1.0
	Total anions	1 to about 170	136 to 170
15	(5) chloride ⁻	0.6 to about 137	81 to 129
	(6) bicarbonate ⁻	0 to about 64	0 to 51
	(7) sigma l-lactate ⁻ / and pyruvate	0 to about 64	0 to 51
20	(8) sigma d-betahydroxy- butyrate /and acetoacetate	0 to about 64	0 to 51
	(9) sigma (6+7+8)	0.4 to about 64	25 to 51
	Total nonionics	about 0 to 625	0 to 305
	(10) carbon dioxide	about 0 to 25	0 to 5
25	(11) osmotically active substances*	about 0 to 600	0 to 300
In Table V solutions the component interrelationships are always such that:			
30	(12) mEq.ratio of HCO ₃ ⁻ / CO ₂	about 0.1/1 to 55/0.1	0.1/1 to 55/0.1
	(13) mEq.ratio of l-lactate ⁻ / pyruvate	about 20/1 to 1/1	10/1 to 5/1
35	(14) mEq.ratio of d-betahydroxybutyrate ⁻ / acetoacetate	about 6/1 to 0.5/1	3/1 to 1.5/1
	(15) mEq.ratio of Na:Cl	about 1.24 to 1.6	1.24 to 1.6

SUBSTITUTE SHEET

57

(16) Milliosmolarity of

Solution

about 260 to 950

260 to 550

(17) pH of Solution

about 5 to 9

5 to 9

*glucose preferred

SUBSTITUTE SHEET

Class II solutions which are particularly suited for use in dialysis (whether hemo- or peritoneal) are subgenerically characterized in Table IV below.

SUBSTITUTE SHEET

Table VI

Class II Solutions Particularly Suited for Dialysis
(Hemo- & Peritoneal)

		Composition at Time of Administration	
		Quantity Range	
Component		(millimoles per liter)	
		broad	preferred
5	Total cations (mEq/L)	about 130 to 170	136 to 155
	(1) sodium ⁺	about 130 to 155	135 to 145
	(2) potassium ⁺	0 to about 5	0 to 4
	(3) calcium ⁺⁺	0 to about 3	0 to 1.7
	(4) magnesium ⁺⁺	0 to about 2	0.3 to 1
10	Total anions (mEq/L)	about 130 to 170	136 to 155
	(5) chloride ⁻	about 81 to 125	86 to 104
	(6) bicarbonate ⁻	0 to about 60	25 to 45
	(7) sigma l-lactate ⁻ /plus pyruvate	0 to about 60	2 to 10
	(8) sigma d-betahydroxybutyrate ⁻ / plus acetoacetate	0 to about 60	1 to 5
20	(9) sum (6+7+8)	about 25 to 60	27 to 55
	Total nonionics	0 to about 525	11 to 280
	(10) carbon dioxide	0 to about 25	0.5 to 2
	(11) osmotically active substance*	0 to about 500	10 to 280
25		In Table VI Solutions, the component interrelationships are always such that:	
30	(12) mEq.ratio HCO ₃ ⁻ / CO ₂	about 0.1/1 to 55/0.1	19/1 to 8/1
	(13) mEq.ratio of L-lactate ⁻ / pyruvate	about 20/1 to 1/1	10/1 to 5/1
	(14) mEq. ratio of Na:Cl	about 1.24 to 1.6	1.36 to 1.5
	(16) Milliosmolarity of Solution	about 260 to 850	280 to 320
	(17) pH of Solutions	about 5 to 9	7.35 to 8
35		*glucose preferred	

SUBSTITUTE SHEET

Class II solutions which are within the scope of Table VI above and which are particularly suited for hemodialysis are subgenerically characterized in Table VII below. As before, each Table VII solution comprises
5 water which as dissolved therein the indicated components in the respective amounts indicated.

Such Class II solutions in Table VII are suitable for use in a hemodialysis process of the generally known and conventional type where renal function
10 of a living mammal is replaced in whole or in part by dialysis. In hemodialysis, portions of the blood of such mammal are continuously passed over one face of a dialysis membrane (which is incorporated preferably a high surface area cartridge-like structure) while the
15 opposed face of such membrane is contacted with a dialysis fluid, thereby to achieve a change in the chemical composition of the body fluids after the so dialyzed blood is returned to the mammal's vascular system. Duration of a conventional hemodialysis can vary,
20 depending upon equipment, conditions, patient condition, and the like, but typically can extend for a time of from about 3 to 5 hours. Optionally, but preferably, the dialysis membrane used in combination with the associated apparatus is such that the blood so passed
25 over such membrane can be pressurized during such passage (typically and conventionally up to about 300 grams per cubic centimeter), thereby to produce what is known in the dialysis art as "ultrafiltration". In the conventional hemodialysis procedure, the dialysis fluid
30 is an aqueous solution which contains dissolved therein the same principal inorganic electrolytes at respective individual concentration levels which approximate such major plasma electrolytes and their concentrations.

In the parent hemodialysis one substitutes for
35 the conventional dialysis fluid a solution of the present invention as above characterized in Table VII. Conventional dialysis equipment can be used, but a

SUBSTITUTE SHEET

deaerator, such as might tend to eliminate dissolved carbon dioxide from a dialysis solution of this invention, should not be present. During use in peritoneal dialysis, a solution of this invention:

- 5 (a) tends to maintain a normal equivalent ratio of sodium cations to chloride anions, and
 - (b) tends to maintain normal cellular and plasma pH, and
 - 10 (c) tends to maintain normal cofactor ratios.
- The total quantity of such solution of this invention used in a given hemodialysis is comparable to the quantities used in prior art fluids employed under the same conditions (typically from about 35 to 160 liters
- 15 of dialysis fluid per hemodialysis per man).

SUBSTITUTE SHEET

Table VII
Class II Solutions Particularly Suited for
Hemodialysis

5	Component	Composition at Time of Administration Quantity Range (millimoles per liter)	
		broad	preferred
10	Total cations (mEq/L)	about 130 to 170	134 to 154
	(1) sodium ⁺	about 130 to 155	132 to 145
	(2) potassium ⁺	0 to about 5	0 to 4
	(3) calcium ⁺⁺	0 to about 3	1 to 1.75
	(4) magnesium ⁺⁺	0 to about 2	0.3 to 0.75
15	Total anions (mEq/L)	about 130 to 170	134 to 154
	(5) chloride ⁻	84 to about 125	93 to 115
	(6) bicarbonate ⁻	0 to about 55	25 to 35
	(7) sigma L-lactate ⁻ / pyruvate	0 to about 55	0 to 12
	(8) sigma D-betahydroxybutyrate ⁻ / acetoacetate	0 to about 55	0 to 5
20	(9) sigma (6+7+8)	about 25 to 55	36 to 42
	Total nonionics*	about 0 to 525*	0 to 12
	(10) carbon dioxide	about 0 to 25	0 to 2
	(11) osmotically active substances**	about 0 to 500*	0 to 10
In Table VII, the component interrelationships are always such that:			
30	(12) mEq.ratio of bicarbonate ⁻ / CO ₂	about 0.1/1 to 55/0.1	18/1 to 35/0.5
	(13) mEq.ratio of L-lactate ⁻ / pyruvate ⁻	about 20/1 to 1/1	10/1 to 5/1
	(14) mEq.ratio of D-betahydroxybutyrate ⁻ / acetoacetate ⁻	about 6/1 to 0.5/1	3/1 to 1.5/1
	(15) mEq.ratio of Na:Cl	about 1.24 to 1.6	1.26 to 1.55
	(16) milliosmolality of Solution	about 260 to 800	260 to 350

SUBSTITUTE SHEET

(17) pH of Solution about 5 to 9 7.35 to 8

*This upper limit used when the solution is being employed in an old type Kolff kidney where pressure cannot be exerted on the dialysis membrane. In a pressurized dialysis system the limit

5 is about 0 to 11mMol/l for glucose; if other nonionics are added, then preferred limit would be below about 20 mMol/l total.

**glucose preferred.

SUBSTITUTE SHEET

Class II solutions which are within this scope of Table VI above and which are particularly suited for peritoneal dialysis are subgenerically characterized in Table VIII below.

5 Such Class II solutions of Table VIII are suitable for use in a peritoneal dialysis process of the generally known and conventional type when renal function of a living mammal is replaced in whole or in part by dialysis. In peritoneal dialysis a quantity of a dialysis
10 fluid is charged into the peritoneal cavity of such mammal for a time sufficient to achieve a change in the chemical composition of body fluids, after which the dialysate is drained or otherwise removed from the peritoneal cavity. Typical residence times for fluid
15 in the peritoneal cavity range from about 1/2 to 1 hour, although longer and shorter times can be employed. Typically, peritoneal dialysis sessions last 4-1/2 hours, but continuous ambulatory peritoneal dialysis has recently been advocated. The patient's own peritoneum
20 serves as a dialysis membrane. In the conventional peritoneal dialysis procedure, the dialysis fluid is, as in the case of a hemodialysis fluid and aqueous solution which contains dissolved therein the same principal inorganic electrolytes and at respective
25 individual concentration levels which approximate those of major plasma electrolytes and their concentrations, except that in the case of peritoneal dialysis fluids a higher concentration of nonionics, such as glucose, is typically employed in order to provide an osmolarity
30 which is greater than that of mammalian plasma, thereby to promote ion and water transfer through the peritoneum, all as known to those skilled in the art. Chronic, so called "ambulatory" peritoneal dialysis may also benefit from these solutions.

35 In the present invention, one substitutes for the conventional dialysis fluid a solution of the present invention as above characterized in Table VIII. During use in peritoneal dialysis, a solution of this invention:

65

- (a) tends to maintain a normal equivalent ratio of sodium cations to chloride anions,
- (b) tends to maintain normal plasma and cellular pH,
- (c) tends to maintain normal cofactor ratios.

5 The quantity of such solution employed is comparable to the quantity used in prior art peritoneal dialysis as is the residence time in the peritoneal
10 cavity.

SUBSTITUTE SHEET

66

Table VIII

1

Class II Solutions Particularly Suited for Peritoneal
Dialysis

5

Compositions at Time of

Administration

Quantity Range

Component

(millimoles per liter)

		broad	preferred
	Total cations	about 130 to 170	135 to 150
10	(1) sodium ⁺	about 130 to 165	130 to 145
	(2) potassium ⁺	about 0 to 5	0 to 4
	(3) calcium ⁺⁺	about 0 to 2	1 to 1.5
	(4) magnesium ⁺⁺	about 0 to 1.5	0.3 to 1
	Total anions	about 130 to 170	135 to 150
15	(5) chloride ⁻	about 81 to 130	93 to 102
	(6) bicarbonate ⁻	about 0 to 55	25 to 30
	(7) sigma L-Lactate ⁻ /plus pyruvate ⁻	about 0 to 55	2 to 12
20	(8) sigma D-betahydroxybutyrate ⁻ / acetoacetate ⁻	about 0 to 55	1 to 5
	(9) sigma (6+7+8)	about 26 to 55	36 to 50
	Total nonionics*	about 40 to 252	84 to 238
	(10) carbon dioxide	about 0 to 25	0 to 2
	(11) osmotically	about 40 to 250	83 to 237
25	active substance		

In Table VIII, the component interrelationships are always such
that:

	(12) mEq.ratio of HCO ₃ ⁻ / CO ₂	about 0.1/1 to 160/1	19/1 to 21/1
30	(13) mEq.ratio of L-lactate ⁻ / pyruvate ⁻	about 20/1 to 1/1	10/1 to 5/1
	(14) mEq. ratio of D-betahydroxybutyrate ⁻ / acetoacetate ⁻	about 6/1 to 0.5/1	3/1 to 1.5/1
35	(15) mEq.ratio of Na:Cl	about 1.24 to 1.6	1.36 - 1.42

* glucose preferred

SUBSTITUTE SHEET

- 1 (16) Milliosmolarity of
 Solution about 310 to 615 350 to 520
 (17) pH of solution about to 8 7.36 to 7.6

EMBODIMENTS

- 5 The following examples are merely illustrative of
the present invention and are not intended as a limitation
upon the scope thereof.

Examples 1 through 27

- 10 The following compositions of this invention illus-
trate electrolyte solutions of Class I (above identified)
which are suitable for intravenous administration to
replace electrolytes and fluid in a human adult patient
at dose rates of, for example, 500ml/patient/24 hour
day. Each solution consists of water which has dissolved
15 therein each of the identified in the respective specific
per liter quantity shown components in the following
Table IX.

- Each solution is here prepared by dissolving
substantially pure selected salt and nonionic material
20 following the teaching of "Date for Biochemical Research",
1969, pp.507-508. Each solution can be made from many
different materials depending upon manufacturing con-
venience, ease of sterilization, cost of raw materials,
and the like; the only requirement is that the final ionic
25 composition of each solution should be as described.

 The footnote for each example in Table IX charac-
terizes the composition and provides a suggested
application or use.

- 30 Also shown in Table IX are further examples of prior
solutions. All solutions are listed as Type 1 a, b, c,
and d, in conformity with the classification herein
developed.

Table IX Class Ia Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} or Ca^{2+} with no Nutrients (Glucose)
Case 1
and No $\text{HCO}_3^-/\text{CO}_2$

Units	Normal	Ia 1	Ia 2	Ia 3	Ia 4	Ia 5	Ia 6
moles	Plasma	"Normal"	"Normal"	Isotonic	Isotonic	Isotonic	Isotonic
-----	<i>N.E.J.M.</i>	0.9% NaCl	0.95% NaCl	NaLactate	NaLact/Pyr	NaLact/Pyr	Na BHB/acac
L fluid	283, 1285	U.S.	U.K.	Salt	Salt	BHB/acac	Salt
	1970						
Na	136 - 145	155	162.5	160.3	155	155	152.5
K	3.5 - 5.0						2.5
Ca	2.1 - 2.6						
free $[\text{Ca}^{2+}]$ [1.06]							
Mg	0.75 - 1.25						
free $[\text{Mg}^{2+}]$ [0.53]							
Σ eq Cations	142.7-153.2	155	162.5	160.3	155	155	155
Cl	100 - 106	155	162.5	108.3	106	106	106
HCO_3^-	26 - 28						
ΣPi	1 - 1.45						
SD_4	0.32 - 0.94						
L - lactate	0.6 - 1.8			52 (d,1)	44	38	
pyruvate					5	5	

68a

Lact/pyr	00	8.8	9.5	
D B OHbutyrate			4.7	35
acetoacetate			2.3	14
B HB/ acac			2.0	2.5
acetate				
Other				
Σ mEq anions	128.7-139.4	155	155	155
Na/Cl	1.28 - 1.45	1.00	1.46	1.44
Glucose or others CO ₂	3.9 - 5.6 0.99 - 1.39			
pH	7.35 - 7.45	5.5 - 6.5	5.5 - 6.5	6.5
Σ mOsm	285 - 295	310	310	310
Use:	I.V. elec- trolyte replacement	same as lal	Used to prevent acidosis	Alternative to la4 cytoplasm & with K mitochondria

1.a.1. Most common electrolyte solution given in U.S. Tends to cause hyperchloremic acidosis because of abnormal Na/Cl ratio.

See Black DAK. Lancet i, 353, 1952.

1.a.2. Used in U.K. and Canada.

1.a.3. Darrow et al. *J Am Med Ass* 143: 365, 432, 1944. Causes redox imbalance.

1.a.4. : : - Solutions in boxes are new in this disclosure.

Table IX Class Ib Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} , Ca^{2+} with HCO_3^- or $\text{HCO}_3^-/\text{CO}_2$ and No Nutrients.

Units	Normal Plasma	I b 1 Isotonic NaHCO_3^-	4 I b 2 Isotonic $\text{NaHCO}_3^-/\text{CO}_2$ + NaLact/pyr	5 I b 3 Isotonic $\text{NaCl} + \text{Ca}$	6 I b 4 Isotonic NaL/P-B/A- $\text{HCO}_3^-/\text{CO}_2$	7 I b 5 Isotonic $\text{NaCl} + \text{Ca}$ with K^+
moles	N.E.J.M.	283, 1285				
-----		Salt				
L fluid	1970					
Na	136 - 145	160.3	155	153	155	152
K	3.5 - 5.0					3
Ca	2.1 - 2.6			1		
free $[\text{Ca}^{2+}]$ [1.06]						
Mg	0.75 - 1.25					
free $[\text{Mg}^{2+}]$ [0.53]						
Z mEq Cations	142.7-153.2	160.3	155	155	155	155
Cl	100 - 106	108.3	106	106	106	106
HCO_3^-	26 - 28	52	27	27	27	27
Z Pi	1 - 1.45					
SO_4	0.32 - 0.94					
L - lactate	0.6 - 1.8		19	19	13	13

69a

pyruvate	3	3	2	2
Lact/pyr	6.3	6.3	6.5	6.5
D B OHbutyrate			5	4
acetoacetate			2.5	3
B HB/ acac			2.5	1.3
acetate				
Other				
Σ aEq anions 128.7-139.4 160.3	155	155	155	155
Na/Cl 1.28 - 1.45 1.48	1.46	1.44	1.46	1.43
Glucose 3.9 - 5.6				
or others				
CO ₂ 0.99 - 1.39 -	1.3	1.3	1.3	1.3
pH 7.35 - 7.45 8.6	7.35	7.35	7.35	7.35
Σ aOsm 285 - 295 321	311	311	311	311

Use:

1 b 1 Darrow et al J Am Med Ass 143: 365, 452, 1944, abnormal pH. Incompatible with Mg²⁺ and Ca²⁺.

Table IX Class Ic Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} or Ca^{2+} with Non-Ionic Nutrients *

Units	Normal	I c 1	I c 2	I c 3	I c 4	8	9	10
osmoles	Plasma	5X	5.25X	Isotonic	Glucose	I c 5	I c 6	I c 7
-----	M.E.J.M.	Dextrose	Glucose	Glucose 2+	Malactate-	Glucose	Glucose +	Redox
L fluid	283, 1285	+ H ₂ O	U.h.	NaCl 1	NaCl	Malact/Pyr-	Ketones+	Balanced
	1970	0.5%				NaCl	NaCl	2 Gluc + 1 NaCl
Na	136 - 145			54.1	53.4	53.4	52.4	53.4
K	3.5 - 5.0							
Ca	2.1 - 2.6							
free [Ca ²⁺] [1.06]								
Mg	0.75 - 1.25						0.5	
free [Mg ²⁺] [0.53]								
osEq Cations 142.7-153.2 0			0	54.1	53.4	53.4	53.4	53.4
Cl	100 - 106			54.1	36.1	36.1	36.1	36.1
HCO ₃	26 - 28							
Pi	1 - 1.45							
SO ₄	0.32 - 0.94							
L - lactate 0.6 - 1.8					17.3 (d.l.)	15.3		10
pyruvate						2		2

70a

CONSTITUTE SHEET

Lact/pyr	00	7.7	5
D B DHbutyrate		12	3.3
acetoacetate		5.3	2
D HB/ acac		2.3	1.65
acetate			
Other			
Eq anions 128.7-139.4	0	53.4	53.4
Na/Cl	1.28 - 1.45	1.48	1.48
Glucose or others	292	195	195
CO ₂	0.99 - 1.39		
pH	7.35 - 7.45	6.5	6.5
Na	285 - 295	302	302
Use:	fluid replacement + nutrients	Corrects redox imbalance in status epilepticus	Alternative also for IC 5

* Common non-ionic nutrients are 5%, 2.5%, 10% glucose. Additional similar fructose and glycerol solutions in over 20 mM amounts are approved by FDA, but not recommended here. (See "Safe Entry Points")

1 c 1 - Most common I.V. fluid given. *Merck Handbook* 1966, p1867. This is combined with isotonic NaCl in many proportions.

1 c 2 - Used in the U.K. and Canada where "isotonic" is different than in the U.S. - presumably. See *Geigy Handbook*, 1970, p 334.

1 c 4 - Prevents hyperchloremia but causes redox imbalance. *Geigy Handbook 1970*, p 334.

4

Table IX. Class 1c (Cont'd)
Case 1

Units	Normal	11 1 c 8	12 1 c 9	13 1 c 13	14 1 c 14	15 1 c 15
moles	Plasma	2L 05W +	11	D 5 W +	D 10 W +	D 5 W +
-----	W.E.J.M.	0.5L Normal	with K	L/P Saline	BHB/Acrac +	Redox
L fluid	283, 1285	Saline +	Redox		Saline	Balance
	1970	Balance				
Na	136 - 145	31	31	154	154	154
K	3.5 - 5.0		5.0			
Ca	2.1 - 2.6					
free [Ca ²⁺] [1.06]						
Mg	0.75 - 1.25					
free [Mg ²⁺] [0.53]						
ΣEq Cations	142.7-153.2	31	36	154	154	154
Cl	100 - 106	22	22	105	105	105
HCO ₃	26 - 28					
Σ Pi	1 - 1.45					
SO ₄	0.32 - 0.94					
L - lactate	0.6 - 1.8	7	10	43		36
pyruvate		1	1.43	6		6

71a

Lact/pyr	7	7	7.2	7
D B OHbutyrate	0.66	1.57		4
acetoacetate	0.33	1.00		3
B HB/ acac	2	1.6	1.5	1.3
acetate				
Other				
Σ mEq anions 128.7-139.4	31	36	154	154
Na/Cl	1.28 - 1.45	1.41	1.47	1.47
Glucose or others	3.9 - 5.6	222.4	278	278
CO ₂	0.99 - 1.39			
pH	7.35 - 7.45	*6.5	*5.5-6.5	*5.5-6.5
Σ mOsm	285 - 295	284	561	561
Use:			Improves I c 10 with Redox & Na/Cl	Improves I c 11 I c 13
			Balance	

I c 8. Improves with normal Na/Cl ratio and redox balance the most common routine I.V. order in the U.S.

I c 9. Replaces 12.5 mEq of the 40 mEq of K⁺ lost/ day when given at the usual rate of 2.5L/ day.

I c 10. Facts and Comparisons Oct '81, p.51, Ippincott, St Louis

I c 11. Facts and Comparisons Oct '81, p.51, Ippincott, St Louis

I c 12. Facts and Comparisons Oct '81, p.51, Ippincott, St Louis

Table IX. Class 1d Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} , or Ca^{2+} plus Non-ionic Nutrients Plus $\text{HCO}_3^-/\text{CO}_2$
Case 1

Units	Normal	16	17	18	19	20	21	22	23
moles	Plasma	1 d 1	1 d 2	1 d 3	1 d 4	1 d 5	1 d 6	1 d 7	1 d 8
-----	<i>N.E.J.M.</i>	$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	L/P $\text{HCO}_3^-/\text{CO}_2$	L/P $\text{HCO}_3^-/\text{CO}_2$	Redox Bal.	Redox Bal.
L fluid	283, 1285	Saline	Saline	Saline	Saline	Saline	Saline	Saline HCO_3^-	Saline HCO_3^-
	1970	+ K	+ K	+ Mg	+ Ca	+ K	+ K	+ 5% Gluc.	+ 2.5% Gluc.
Na	136 - 145	155	155	155	155	145	145	141	140
K	3.5 - 5.0	5				4	4		4
Ca	2.1 - 2.6				1.5				
free $[\text{Ca}^{2+}]$ [1.06]									
Mg	0.75 - 1.25			1.0					
free $[\text{Mg}^{2+}]$ [0.53]									
Σ Eq Cations 142.7-153.2		155	160	156	158	145	149	141	144
Cl	100 - 106	107	107	107	107	106	106	100	104
HCO_3^-	26 - 28	48	53	49	51	29	29	29	29
2 Pi	1 - 1.45								
SO_4	0.32 - 0.94								
L - lactate	0.6 - 1.8					8.8	12.5	7	7
pyruvate						1.2	1.5	1	1
Lact/pyr						7.3	8	7	7

72a

CONSTITUTE SHEET

	155	160	156	158	145	149	141	
D B OHbutyrate								2
acetoacetate								1
B HB/ atac								2
acetate								
Other								
Z mEq anions 128.7-139.4	155	160	156	158	145	149	141	144
Na/Cl	1.28 - 1.45	1.45	1.45	1.45	1.37	1.37	1.41	1.35
Glucose	3.9 - 5.6	10	10	10	10	10	278	139
or others	0.99 - 1.39	2.75	2.71	2.74	1.45	1.45	1.45	1.45
CO ₂	2.7	(optional)						
pH	7.35 - 7.45	7.35	7.35	7.35	7.4	7.4	7.4	7.4
Z mOsm	285 - 295	320	322	328	290	298	560	427
Use:	Improves normal NaCl leaves patient	Replaces K loss	Mg ²⁺ does not precipitate	Ca ²⁺ does not ppt. as with HCO ₃ ⁻ alone.				

Table IX Class 1d Solutions Containing 1 or 2 Cations, to which is added $\text{HCO}_3^-/\text{CO}_2$ and Non-ionic Nutrients
Case 1 (Cont'd)

Units	24	25	26	27
Normal	1 d 9	1 d 10	1 d 11	1 d 12
Plasma	2L D5W	2L D5W	R.B. Saline Like 1d11	
M.E.J.M.	+ 0.5L R.B.	+ 0.5L R.B.	with K & but BHB acid	
283, 1285	Saline	Saline + K	2.5% Gluc. & added to make	
L fluid			No added CO_2 CO_2 in situ	
Na	136 - 145	28.2	140	140
K	3.5 - 5.0	5	4	4
Ca	2.1 - 2.6			
free $[\text{Ca}^{2+}]$ [1.06]				
Mg	0.75 - 1.25			
free $[\text{Mg}^{2+}]$ [0.53]				
Σ Eq Cations	142.7-153.2	28.2	144	144
Cl	100 - 106	20	104	104
HCO_3	26 - 28	5.8	10.8	29
Σ Pi	1 - 1.45			
SO_4	0.32 - 0.94			
L - lactate	0.6 - 1.8	1.4	1.4	5
pyruvate		0.2	0.2	1

73a

Lact/pyr	7	7	7	7
D B Dihbutyrate	0.4	0.4	2	2
acetoacetate	0.2	0.2	1	1
B HB/ acac	2	2	2	2
acetate				
Other				* 2 Hlactate + 2 d B hydroxybutyric acid
Σ mEq anions 128.7-139.4	28.2	33.2	144	144
Na/Cl	1.28 - 1.45	1.41	1.35	1.35
Glucose or others	3.9 - 5.6	222.4	139	139
CO ₂	0.99 - 1.39	0.54	2	2
pH	7.35 - 7.45	7.4	7.4	7.4
Σ mOsm	285 - 295	279	289	427
Use:	Replaces & Replaces 21 D5W & K loss 0.5l Normal Saline			

1 d 11 * L Lactic acid is added instead of CO₂ to generate CO₂ in situ.

1 d 12 * D B Hydroxybutyric acid is added to generate CO₂ in situ.

INSTITUTE SHEET

1 Examples 28 through 41

 The following compositions of this invention
illustrate electrolyte solutions of Class II (above
identified) which are suitable for (a) intravenous use
5 to replace electrolytes and fluid (b) providing parenteral
nutrition in a human adult patient, (c) peritoneal
dialysis, and (d) hemodialysis. Dose rates can vary.
Each solution consists of water which has dissolved
therein each of the identified components in the respec-
10 tive specified concentrations per liter quantity shown
in the following Table X. Each solution is prepared by
conventional procedures. (See text of Examples 1 through
27).

 The footnote for each example in Table X charac-
15 terizes the composition and provides a suggested appli-
cation or use.

 These compositions demonstrate, as do Tables V
through VIII (above), that there is no essential
compositional difference between these various
20 solutions.

 Table XI shows prior art hemodialysis fluids for
comparison purposes in dialyzing a human adult patient
using, for example, an apparatus as described by
Miller J.H., Schinaberger J.H., Kraut J.A., and
25 Gardner P.S., Trans. Am. Soc. Artif. Intern. Organs 25,
404-408, 1979.

 In these solutions which contain dissolved CO₂,
no daerator should be used on the dialysis equipment.

30

Table X Class 2a-Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells, Containing No $\text{HCO}_3^-/\text{CO}_2$ and No Glucose; eg. after S.J. Ringer, *Physiol* 4: 29, 223, 1865, and 7: 291, 1886.

Units	Normal Plasma	2. a. 1. Ringer's Injection	2. a. 2. Lactated Ringer's	2. a. 3. Lactated Ringer's (Commercial) U.S.	2. a. 4. Acetated Ringer's	2. a. 5. Lact/Actet Ringer's	28 2. a. 6. Lact/Pyr Ringer's	29 2. a. 7. dB-HB/acac Ringer's	30 2. a. 8. Redox Balanced Ringer's
miles	W.F.J.H. 283, 1285	U.S.							

L fluid	1970								
Na	136 - 145	147	129.8	130	130	140	130	130	130
	*(137-145)								
K	3.5 - 5.0	4	5.4	4	4	10	4	4	4
Ca	2.1 - 2.6	2.5	0.9	1.5	1.5	2.5	1.5	1.5	1.5
free $[\text{Ca}^{2+}]$	[1.06]								
Mg	0.75 - 1.25		1.0			1.5			
free $[\text{Mg}^{2+}]$	[0.53]								
2 aEq Cations	142.7-153.2	156	139	137	137	158	137	137	137
Cl	100 - 106	156	111.8	109	109	103	96	96	96
	*(100-110)								
HCO_3^-	26 - 28								
ΣPi	1 - 1.45								
SO_4	0.32 - 0.94								
L - lactate	0.6 - 1.8		27.2 (d,1)	28 (d,1)		27.5 (d,1)	35.9		30
pyruvate							5.1		4

75a

Lact/pyr	00	00	00	7	7.5
D B OHbutyrate					
acetoacetate				27.3	5
B HB/ acac				13.7	2
acetate		28	27.5	2	2.5
Other					
Σ anions	128.7-139.4	139	137	137	137
Na/Cl	1.28 - 1.45 ±(1.245-1.45)	1.16	1.19	1.35	1.35
Glucose or others	3.9 - 5.6				
CO ₂	0.99 - 1.39				
pH	7.35 - 7.45				
Σ anion	285 - 295	309	276	272.5	272.5
Use:	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid
				Improves 2 a 3.	Improves 2 a 4
					Improves 2a3, 2a6, 2a7.

† *M.I.H. Path & Blood Bank Guide, Revised Nov 1, '82.*

2. a. 1. *Facts and Comparisons* p50, Oct '81, Lippincott

2. a. 2. *Hartmann AF. J. Am. Med. Ass.* 103: 1349, 1934.

2. a. 3. *Facts and Comparisons* p50, Oct '81, Lippincott. Widely used in blood product administration and surgery

2. a. 4. *Facts and Comparisons* p50, Oct '81, Lippincott.

2. a. 5. *Fox et al. J. Am. Med. Ass.* 148: 827, 1952. Corrects abnormal Na/Cl ratio but by use of pathogenic organic anions.

SUBSTITUTE SHEET

Table X Class 2a Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells, Containing No $\text{HCO}_3^-/\text{CO}_2$ and No Glucose; eg. after S.J. Ringer, *Physiol* 4: 29, 223, 1883, and 7: 291, 1886.

Units	Normal Plasma	2. a. 1. Ringer's Injection U.S.	2. a. 2. Lactated Ringer's	2. a. 3. Lactated Ringer's (Commercial) U.S.	2. a. 4. Acetated Ringer's	2. a. 5. Lact/Acet Ringer's	28	29	30
mmoles	W.F.J.M. 283, 1285						2. a. 6. Lact/Pyr Ringer's	2. a. 7. d8-HB/acac Ringer's	2. a. 8. Redox Balanced Ringer's
L fluid	1970								
Na	136 - 145	147	129.8	130	130	140	130	130	130
K	*(137-145) 3.5 - 5.0	4	5.4	4	4	10	4	4	4
Ca	2.1 - 2.6	2.5	0.9	1.5	1.5	2.5	1.5	1.5	1.5
free $[\text{Ca}^{2+}]$ [1.06]									
Mg	0.75 - 1.25		1.0			1.5			
free $[\text{Mg}^{2+}]$ [0.53]									
Σ aEq Cations	142.7-153.2	156	139	137	137	158	137	137	137
Cl	100 - 106	156	111.8	109	109	103	96	96	96
HCO_3^-	*(100-110) 26 - 28								
Σ Pi	1 - 1.45								
SO_4	0.32 - 0.94								
L - lactate	0.6 - 1.8		27.2 (d,1)	28 (d,1)		27.5 (d,1)	35.9		30
pyruvate							5.1		4
Lact/pyr			00	00		00	7		7.5

Table X. Class 2a (Cont'd) Solutions with **Bold** numbers and in boxes are new disclosures.

Units	Normal Plasma H.E.J.M. 283, 1285 1970	31 2 a 9 Redox Balanced Ringer's & High K	2 a 10 Ionosol D-CH (Abbott)	2 a 11 Plasmalyte (Travenol)	2 a 12 Isolyte S (McGaw) PolymonicR148 (Cutter)	2 a 13 Isolyte E (McGaw)	2 a 14 Delbecco's Pi Buffered Saline	2 a 15 Krebs Ringer Phosphate
Na	136 - 145	140	138	140	140	140	152	150.76
K	3.5 - 5.0	10	12	10	5	10	4.17	5.92
Ca free [Ca ²⁺] [1.06]	2.1 - 2.6	1.0	2.5	2.5		2.5	0.9	2.54
Mg free [Mg ²⁺] [0.53]	0.75 - 1.25	0.5	1.5	1.5	1.5	1.5	0.45	1.18
z aEq Cations 142.7-153.2		153	158	158	148	158	159.15	164.12
Cl	100 - 106	103	108	103	98	103	140.5	131.51
HCO ₃	26 - 28							
Σ Pi	1 - 1.45						9.8	17.38
SO ₄	0.32 - 0.94						0.45	1.18
L - lactate	0.6 - 1.8	38	50 (d,1)	8 (d,1)				
pyruvate		5						
Lact/pyr		7.6	00	00				

-77a-

[illegible]

- 2 a 10. *Facts and Comparisons* Oct '81, p 50
- 2 a 11. *Facts and Comparisons* Oct '81, p 50
- 2 a 12. *Facts and Comparisons* Oct '81, p 50
- 2 a 13. *Facts and Comparisons* Oct '81, p 50
- 2 a 14. Delbecco R, Vogt M. *J Exp Med* 99: 167
- 2 a 15. Krebs NA. *Hoppe-Seyle's Z Physiol Chem*

Table X. Class 2b Electrolyte Fluids Containing 3 to 4 Cations Suitable for Contacting Cells Also Containing $\text{HCO}_3^-/\text{CO}_2$ and No Glucose after Krebs HA & Henseleit KA, Hoppe-Seyler's Z Physiol Chem 210: 33-66, 1932.

Units	Normal	2 b 1	32	33	34	35	36
moles	Plasma	Krebs	2 b 2	2 b 3	2 b 4	2 b 5	2 b 6
-----	N.E.J.M.	Henseleit	Redox Bal- anced	Redox Bal- anced	High HCO_3^- Ringer sine Lactate	L/P Ringer's Ketones	Ringer's Ketones
L fluid	283, 1285 1970		Ringer's & $\text{HCO}_3^-/\text{CO}_2$	Ringer's & $\text{HCO}_3^-/\text{CO}_2$ & Mg	RedoxBalance $\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$
Na	136 - 145	143	130	136	136	130	130
K	3.5 - 5.0	5.9	4	4	4	4	4
Ca	2.1 - 2.6 free $[\text{Ca}^{2+}]$ [1.06]	2.5	1.5	1	1	1.5	1.5
Mg	0.75 - 1.25 free $[\text{Mg}^{2+}]$ [0.53]	1.2		0.5	0.5		
Σ Eq Cations	142.7-153.2	156.3	137	143	143	137	137
Cl	100 - 106	127.8	96	100	100	96	96
HCO_3^-	26 - 28	25	29	29	43	29	29
Σ Pi	1 - 1.45	1.18					
SO_4	0.32 - 0.94	1.2					
L - lactate	0.6 - 1.8		7	9		10.5	
pyruvate			1	1		1.5	

SUPPLEMENT SHEET

Lact/pyr	7	9	7
D B DIButyrate	3	3	8
acetoacetate	1	1	4
B HB/ acac	3	3	2
acetate			
Other			
Σ mEq anions 128.7-139.4	137	143	137
Na/Cl	1.28 - 1.45	1.12	1.35
Glucose	3.9 - 5.6		
or others			
CO ₂	0.99 - 1.39	1.24	1.5
pH	7.35 - 7.45		7.4
Σ mOsm	285 - 295	308	274
Use:	Tissue incubation, organ perfusion	To replace For blood For Rx of acidosis to 2 b 2	Alternate to 2 b 5

2 b 2 to 2 b 6. All these solutions would be suitable, given added glucose, for peritoneal dialysis, ie like class 2 c. As it is, these solutions would improve existing hemodialysis.

Table X. Class 2c Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells Containing No $\text{HCO}_3^-/\text{CO}_2$ to which are Added Non-ionic nutrients such as Glucose, Fructose, Glycerol etc.

Units	Normal	2 c 1	2 c 2	2 c 3	2 c 4	2 c 5	2 c 6	2 c 7
Plasma		Lactated	1/2 Strenght	Acetated	Ionosol B	Dianeal	Peritoneal	Dianeal
samples	H.E.J.M.	Ringer's & 5% Lactated	Ring+ 2.5% 5% Glucose	Ringers & 5% Glucose	5% & 5% Glucose	& 1.5% Glucose	Dialysis 4.25% Gluc	K-141 & 4.25% Glucose
-----	283, 1285	Glucose	Ring+ 2.5% 5% Glucose	5% Glucose	6% Glucose	6% Glucose	(Travenol)	(Travenol)
L fluid	1970				(Abbott)		(Am. McGaw)	
Na	136 - 145	130	65	130	57	141	141.5	132
K	3.5 - 5.0	4	2	4	25			4
Ca	2.1 - 2.6	1.5	0.75	1.5		1.75	2.0	1.875
free [Ca2+]	[1.06]							
Mg	0.75 - 1.25				2.5	0.75	0.75	0.75
free [Mg2+]	[0.53]							
2 mEq Cations	142.7-153.2	137	68.5	137	87	146	147	141
Cl	100 - 106	109	55	109	49	101	102.5	106
HCO_3^-	26 - 28							
2 Pi	1 - 1.45							
SO_4	0.32 - 0.94							
L - lactate	0.6 - 1.8	28 (d,1)	14 (d,1)		25 (d,1)	45 (d,1)		35 (d,1)
pyruvate								

6.5 H_2PO_4^-

-79a-

Lact/pyr	00	00	00	00	00	00
D B Dihbutyrate						
acetoacetate						
B HB/ acac						
acetate		28			44.5	
Other						
Σ aEq anions 128.7-139.4	137	69	137	87	146	141
Na/Cl	1.28 - 1.45	1.18	1.19	1.16	1.40	1.25
Glucose	3.9 - 5.6	139	278	278	83	236
or others						
CO ₂	0.99 - 1.39					
pH	7.35 - 7.45					
Σ mOsm	285 - 295	524?	263	523	366	494
		±(550.5)				
Use:	I.V. therapy I.V. therapy I.V. therapy Parenteral Peritoneal Peritoneal					
	for dehydra- same as same as nutrition dialysis dialysis					
	tion 2 c 1 2 c 1					

* 2 c 1. Facts and Comparisons Oct '81, p 52. The osmolality listed by the reference appears to be incorrect at 524 mOsm.

The correct osmolality appears to be 550.5 mOsm.

2 c 2 - 2 c 3. Facts and Comparisons Oct '81, p52. Lippincott, St Louis

2 c 4. Facts and Comparisons Oct '81, p52. Lippincott, St Louis

2 c 5 - 2 c 7. Facts and Comparisons Oct '82, p704, Lippincott, St Louis

Table X. Class 2c (Cont'd)

Units	Normal Plasma	37 2 c 8	38 2 c 9
mmoles	M.E.J.H.	L/P,BHD/Acac Na/Cl, L/P	Ringer's Balanced
-----	283, 1285	& 5X Gluc	Ringer's
L fluid	1970		& 5X Gluc
Na	136 - 145	130	130
K	3.5 - 5.0	4	4
Ca	2.1 - 2.6	1.5	1.5
free [Ca ²⁺] [1.06]			
Mg	0.75 - 1.25		
free [Mg ²⁺] [0.53]			
ZmEq Cations	142.7-153.2	137	137
Cl	100 - 106	104	96
HCO ₃	26 - 28		
Σ Pi	1 - 1.45		
SO ₄	0.32 - 0.94		
L - lactate	0.6 - 1.8	24.5	35.9
pyruvate		3.5	5.1

-80a-

Lact/pyr	7	7
D B OHbutyrate	3	
acetoacetate	2	
B HB/ acac	1.5	
acetate		
Other		
Z mEq anions 128.7-139.4	137	137
Na/Cl	1.28 - 1.45	1.24 1.35
Glucose	3.9 - 5.6	278
or others		
CO ₂	0.99 - 1.39	
pH	7.35 - 7.45	
Z mOsm	285 - 295	550.5 550.5
Uses:	Improved 2 a 6 2 c 1, with with Gluc. redox bal- Normal BHB/Atac ance and normal normal Na/Cl ratio Na/Cl	

SUBSTITUTE SHEET

Table X. Class 2d Electrolyte Fluids for Contacting Living Cells Containing 3 to 4 Cations plus Non-Ionic Nutrients plus $\text{HCO}_3^-/\text{CO}_2$.

Units	Normal	2 d 1	2 d 2	39	40	41
moles	Plasma	Krebs	Tyrod's	2 d 3	2 d 4	2 d 5
-----	M.E.J.M.	Serum	Solution	Veech's	Veech's	Veech's
L fluid	283, 1285	Substitute		Redox	R.B.-Salt	R.B.-Salt
	1970			Balanced	sine Pi	sine Pi
				Salt Solution	5% Glucose	
Na	136 - 145	141	151.54	142	140.4	141
K	3.5 - 5.0	5.93	5.9	4.5	4.5	4
Ca	2.1 - 2.6	2.54	1.8	1.1	1.1	1.1
free $[\text{Ca}^{2+}]$	[1.06]			[1.06]		
Mg	0.75 - 1.25	1.18	0.45	0.56	0.56	0.56
free $[\text{Mg}^{2+}]$	[0.53]			[0.53]		
$\Sigma \text{mEq Cations}$	142.7-153.2	154.37	162.07	149.82	148.2	148.3
Cl	100 - 106	104.8	147.8	102	102	102
HCO_3^-	26 - 28	24.9	11.9	29	29	29
ΣPi	1 - 1.45	1.23	1.228	1.14		
				[0.71]		
SO_4	0.32 - 0.94	2.36				
L - lactate	0.6 - 1.8		1.33	10.7	10.7	10.8
pyruvate		4.9	0.09	1.5	1.5	1.5

-81a-

Lact/pyr	-	14.8	7	7	7
D B Dibutyrate			3	3	3
acetoacetate			2	2	2
B HB/ acac			1.5	1.5	1.5
acetate					
Other	2.45 glutamate ₂ 5.4 fumarate				
Σ mEq anions	128.7-139.4 154.47	162.81	149.82	148.2	148.3
Na/Cl	1.28 - 1.45 1.35	1.03	1.39	1.38	1.38
Glucose or others	3.9 - 5.6 9.2	5.45	10	277	10
CO ₂	0.99 - 1.39 1.0	1.17	1.45	1.45	1.45
pH	7.35 - 7.45 7.4	7.1	7.40	7.40	7.40
Σ mOsm	285 - 295 308.2	328	308.6	573.2	306.4
Use:	Media for tissue slices	For liver perfusion	For I.V. or for perito- general use neal dial. & peritoneal to replace or I.V. dialysis 2 b 1 & 2 d 1		

2 d 1. Krebs HA. *Biochem Biophys Acta* 4: 249-269, 19502 d 2. Tyrode NJ. *Arch int Pharmacodyn* 20: 205, 1910. # For use in liver perfusion with albumin seeSchimassek H. *Biochem Z* 336:460, 1963

2 d 3. # The apparent charge on sum Pi in the presence of these cations is about 1.46 not 1.8 presumably due to cation binding.

SUBSTITUTE SHEET

Table XI. Prior Art Hemodialysis Fluids. For recent discussion see Parsons FN, Stewart WK. Composition of Dialysis Fluid. In: *Replacement of Renal Function by Dialysis* (Drucker M, Parsons FN, Maher JP, eds.) Martinus Nijhoff, Hingham, pp 148-170, 1983.

Units	Normal	2 d 6	2 d 7	2 a 16	2 a 17	2 a 18	2 a 19	2 b 2	2 b 3
Plasma		Kolff	Brigham	Scribner's	Commercial	Bjaelder	Bjaelder	Kraut	COBE
N.F.J.H.		1947	1952	Acetate	Acetate	"Low" Acet.	"High" Acet.	HCO ₃ -Acetic	HCO ₃ -Acetic
283, 1285				1964	1981	1981	1981	Acid, 1981	Acid
L fluid	1970								
Na	136 - 145	126	140	135	140	134	136	140	135
K	3.5 - 5.0	5.6	4	1.5	2	2.2	2.2	2	2
Ca	2.1 - 2.6	1.0	1.25	1.25	0.875	1.04	1.91	1.75	1.5
free [Ca ²⁺] [1.06]									
Mg	0.75 - 1.25		0.5	0.5	0.375	0	0	-	0.375
free [Mg ²⁺] [0.53]									
mEq Cations	142.7-153.2	133.6	147.5	140	144.5	139.88	142.02	145.5	140.75
Cl	100 - 106	109	120.7	105	106	107.28	103.82	107	106.5
HCO ₃	26 - 28	23.9	26.8					33	33
Pi	1 - 1.45								
SO ₄	0.32 - 0.94								
L - lactate	0.6 - 1.8								
pyruvate									

1

EXAMPLE 42

The following example illustrates usage of Class I solutions for electrolyte and fluid therapy.

5 The most commonly used electrolyte solution used today, by those skilled in the art, is so called "physiological" salt, or "normal saline" by which is means 0.9% NaCl in H₂O in the U.S. or 0.95% NaCl in H₂O in the United Kingdom. (See Table IX solutions 1a1 and 1a2 respectively). These solutions, wherein the 10 milliequivalent ratio of Na/Cl is 1, are distinctly different from normal human plasma wherein the ratio of Na/Cl ranges from 1.28 to 1.45 (N.E.J.M. 283, 1285, 1970). Infusion of such solutions has long been recognized to be undesirable leading to a pathological condition known 15 as "hyperchloremic acidosis". (See Black D.A.,., Lancet 1, 353, 1953, and Harrison's Textbook of Medicine, pp 230 to 236, 1983). The degree of the pathology induced by solutions where the ratio of Na/Cl is below the ratio 1.28-1.45 depends upon:

- 20 1) the quantity of solution infused relative to the volume and electrolyte content of the extra-and intracellular H₂O volume of the cells being contacted;
- 2) the rate of infusion of solutions;
- 25 3) the degree of existing pathology in the organism being contacted with such fluid;
- 4) the efficiency of the kidney in excreting the excess of Cl⁻ and Na⁺ being administered.

In this example, the replacement of plasma H₂O 30 and salt content in the rat serves as a model stimulating the situation which might occur in a human patient when a severe burn over 50% of the body exists resulting in the loss of plasma H₂O and electrolytes into transudates and blisters over the surface of damaged skin. Three 35 solutions for therapy will be used: standard 0.9%

- 1 aqueous NaCl (composition 1a1 of Table IX), standard
lactated Ringer's U.S. (composition 2a3 of Table X) and
a modified redox-balanced Ringer's Lactate solution
containing, with near-equilibrium couples, (l-lactate⁻/
5 pyruvate⁻ and D-betahydroxybutyrate⁻/acetoacetate⁻),
HCO₃⁻/CO₂ (composition 2b2 of Table X)
in accord with the present invention. The composition
of the 3 fluids are given in Table XIII below.

10

(Electro2)

Table XIII - Composition of Fluids

Units	Normal Plasma M.F.J.M. 283, 1285 1970	1 a 1 Isotonic NaCl	2 a 3 Lactated Ringer's	2 b 2 R-6 Lactated Ringer's HCO ₃ /CO ₂
Na	136 - 145	155	130	130
K	3.5 - 5.0		4	4
Ca free [Ca ²⁺] [1.06]	2.1 - 2.6		1.5	1.5
Mg free [Mg ²⁺] [0.53]	0.75 - 1.25			
Σ aEq Cations	142.7-153.2	155	137	137
Cl	100 - 106	155	109	96
HCO ₃	26 - 28			29
Σ Pi	1 - 1.45			
SO ₄	0.32 - 0.94			
L - lactate	0.6 - 1.8		28 (d,1)	7
pyruvate				1
Lact/pyr			∞	7

85a

D B Dihutyrate			3
acetoacetate			1
B HB/ acac			3
acetate			
Other			
Σ aEq anions 128.7-139.4	155	137	137
Na/Cl	1.28 - 1.45	1.00	1.35
Glucose or others	3.9 - 5.6		
CO ₂	0.99 - 1.39		1.5
pH	7.35 - 7.45	6.0	7.4
Σ aOsa	285 - 295	310	274

CULCOTITUTE SHEET

1 METHODS

250 fed male Wistar rats are each anesthetized and systematically burned with gasoline over approximately the lower 50% of the body surface. A blood sample is
5 taken from each rat prior to administration of the burn, and then again two hours after the burn from a venous canula inserted into the saphenous vein. Each animal is placed in a restraining case.

In the opposite saphenous vein, a canula is inserted
10 to measure plasma electrolyte content. Five minutes after the administration of each electrolyte solution, blood is drawn for electrolyte analysis. Each rat's liver is removed, freeze clamped and the redox and phosphorylation states of liver measured by the
15 methods previously described by Veech et al. (J. Biol. Chem. 254, 6538-6547, 1979).

RESULTS AND DISCUSSION

It is observed that 1/2 hour after the gasoline burn, a series of weeping blisters develop over
20 the lower 1/2 of each rat's body. The volume of the transudate within these blisters is estimated by measurement of area and thickness to contain 4ml of transudate or $(250 \times 0.07 = 17.5 \text{ ml blood volume})$ or about 40% of the rat's average total plasma volume.
25 This deduction is confirmed by measurement of the rat hematocrit which is 55% while the Na^+ is 155 millimoles per liter plasma and Cl^- is 110 millimoles per liter plasma due to fluid loss. In the untreated controls rats, the hematocrit is 44%. Each treated
30 animal's blood pressure is falling, heart rate is increasing, and urine output ceases.

Each treated animal is judged to be in hypo-volemic shock and 6mls of the three different solutions are infused, by venous canula, over the
35 next 10 minutes, into three different animals.

87

- 1 Five minutes after completion of the infusion, electrolytes are drawn from the canula, the animals sacrificed, and the liver freeze clamped. The average blood electrolyte level, in each of the three groups of animals so infused, is shown in Table XIV below.

5

SUBSTITUTE SHEET

Table XIV Composition of Plasma After Infusion

Units m moles/ L fluid	Normal Plasma H.E.J.M. 283, 1285, 1970	1a1 Isotonic NaCl	2a3 Lactated Ringers	2b2 R-B Lactated Ringers HCO ₃ / CO ₂
Na	135-145	150	143	138
K	3.5-5.0	5	5	5
Ca free [Ca ²⁺]	2.1-2.6 [1.06]	2.0	2.2	2.5
Mg free [Mg ²⁺]	0.75-1.25 [0.53]	1.0	1.0	1.0
Σ meq Cations	142.7-153.2	158	153.2	147.5
Cl	100-106	123	105	102
HCO ₃	26-28	18	13	27
Σ Pi	1 - 1.45	1.5	1.2	1
L-lactate	0.6-1.8	5.0	21	5
pyruvate		0.3	1.0	0.7
Lact/pyr			21	7
D-B-OH butyrate				2
acetoacetate				0.7
BHB/acac				3
acetate				
others				
Σ meq anions	128.7-139.4	146.3	141.2	138.65
Na/Cl	1.28-1.45	1.22	1.34	1.36
Glucose or others	3.9-5.6	8.2	10	7
CO ₂	0.99-1.39	1.14	0.82	1.35
pH	7.35-7.445	7.30	7.30	7.4
Σ m Osm	285-295			

SUBSTITUTE SHEET

1 Having now fully described the invention, it will be
apparent to one of ordinary skill in the art that many
changes and modifications may be made thereto without
department from the spirit or scope of the invention as
5 set forth herein.

It is observed that the animals given 1a1 (0.9%
saline) solution each have hyperchloremic acidosis with
a Na/Cl ratio of 1.22 and plasma pH of 7.30.
The animals given solution 2a3 Ringer's Lactate solution
10 each have lactic acidosis with a plasma pH of 7.3 and
an elevated [lactate]/[pyruvate] ratio. Both groups of
these animals have low serum HCO_3 and have a compensa-
ted metabolic acidosis which requires that they hyper-
ventilate off their CO_2 . In contrast, the animals given
15 solution 2b2 (Redox-balanced Ringers Lactate with HCO_3 /
 CO_2) each have a normal [lactate]/[pyruvate] ratio, a
normal HCO_3 /[CO_2] ratio and a normal plasma pH.
More importantly, each of these animals achieves a
replacement of H_2O and electrolytes as required for
20 continued life, but without inducing an abnormal Na/Cl
ratio, an abnormal redox state, or an abnormal
phosphorylation potential. No change in respiratory
pattern is observed in the grave life-threatening situ-
ation. Solution 2b2 is then an improvement over the
25 state of the art.

In Table 3 is given the results of the freeze clamp-
ing of the liver to illustrate the effects of these
solutions on the nucleotide ratios in liver cells. These
results indicate that only in the liver cells of the
30 rats treated with the redox-balanced Ringer's lactate
solution (Table X, solution 2b2) of this invention do
these ratios approach normal values. Here, it is seen
that administration of Na/Cl in 1:1 ratio leads to no
change in the cytoplasmic [NAD]/[NADH] but does cause
35 an increase in the cytoplasmic [ATP]/[ADP][Pi]. With

1 no intention to be bound by theory, the elevation of
[ATP]/[ADP][Pi] would be expected from equation 7 given
in another section. The conventional Ringer's lactate
(2a3) gives a profound and pathological decrease in
5 the cytoplasmic $[NAD^+]/[NAD]$ to levels associated with
alcoholic fatty liver. There is, of course, a
predictable falls in the [ATP]/[ADP][Pi], since the
redox state of the cytoplasmic NAD-couple is directly and
inversely linked to the cytoplasmic [ATP]/[ADP][Pi]
10 ratio as equation 5 shows.

In contract, the new Redox Balanced Ringer's Lac-
tate solution of the present invention does not change
the cytoplasmic $[NAD^+]/[NADH]$ from out of the normal
range and causes no change in the [ATP]/[ADP][Pi].
15 Replacement of needed H_2O and electrolytes has been
accomplished without inducing acidosis or any other
recognized pathologic effects which can be
demonstrated by using NaCl in 1:1 ratio or standard
Ringer's Lactate in this simulation of a very common
20 clinical situation.

Example 42
Case 1

Table XV. Metabolite Contents of Freeze-Clamped Rat Liver in Rats After Infusion with Normal Saline, Ringer's Lactate, and Redox Balanced Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$

Values are in umoles/g wet weight.

	Normal Rat Solution	0.9% NaCl Infusion 1.a.1	Ringer's Lactate 2.a.3	New R-B Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$ 2.b.2
Glucose	7.3	8.0	13	8
Glucose 6-P	0.12	0.18	0.26	0.16
Dihydroxy- acetone-P	0.029	0.051	0.078	0.039
3-Phospho- glycerate	0.309	0.369	0.56	0.35
L-Lactate	0.444	0.812	14.8	5.2
Pyruvate	0.086	0.165	0.70	0.74
L-Lactate/pyr	5.16	4.92	21	7.00
3-PG/DHAP	10.65	7.24	7.14	8.93

Example 42
Case 1

Table XVI Co-Factor Ratios of Freeze-Clamped Liver of Rat After Infusions with 0.9% Normal Saline, Ringer's Lactate, and Redox-Balanced Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$

	Normal Rat	0.9% NaCl Infused Rat 1.a.1	Ringer's Lactate Infused Rat 2.a.3	New R-B Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$ 2.b.2
Free Cytoplasmic [NAD ⁺]/[NADH]	1750	1790	429	1290
Free Cytoplasmic $\frac{[\Sigma\text{ATP}]}{[\Sigma\text{ADP}][\Sigma\text{F}_1]} \text{ M}^{-1}$	14,000	20,900*	5,000*	12,000

* indicates change is significant at $p > 0.05$.

1

Example 43

Use of Solutions for Parenteral Nutrition

The procedure used is identical to that utilized by Woods, Eggleston and Krebs in Biochem. J. (1970) 119, 501-510.

5

Animals and Diets

Female Wistar rats, each weighing 170-215g, are obtained and are fed on a standard small-animal diet.

Reagents

10

D-Glyceraldehyde, 1- -Glycerophosphate (dicyclohexyl-ammonium salt) having a purity of 96% of the calculate L-form and other substances, nucleotides, coenzymes, and crystalline enzymes.

Liver Perfusion

15

The method of liver perfusion used is that described by Hems, Ross, Berry & Krebs (1966). The perfusion medium is the physiological saline (Krebs & Henseliet, 1932), containing washed aged human erythrocytes. The bovine serum albumin is dialyzed as a 10% solution (at 4°C) against three changes of physiological saline (Krebs-Henseleit) and gassed with CO₂ + O₂ (5:95).

20

The perfusion medium described by Hems et al. (1966) is used, which contains initially about 1 mM l-lactate [0.87 + 0.05 S.E.M. (14) umol/ml] derived from the erythrocytes. To decrease the initial lactate concentration, the erythrocytes are washed five times with ten times their volume of physiological saline. This lowers the initial lactate concentration in the perfusion medium to 0.23 ± 0.02 S.E.M. (16) umol/mol. The medium is gassed with CO₂ + O₂ (5:95) during perfusion.

30

Into the perfusion of 150ml is added a sufficient quantity of two parenteral nutrient solutions, one containing 10 mM D-Fructose from a commercial source (5% Fructose in Electrolyte #75, Travenol, Facts and

35

- 1 Comparison, August '83, p52b) and a new parenteral solu-
tion composition using glucose in place of fructose, a
normal Na:Cl ratio, redox-balanced lactate, pyruvate
and excess K as does Electrolyte #75. Glucose
5 enters the metabolic sequence at a "safe entry" point
as herein defined. The composition of each solution is
given in Table XVII below.

Sampling of Liver

- For the analysis of liver, samples are rapidly fro-
10 zen in vivo or during perfusion, by using the deep cooled
clamps of Wollenberger, Ristau & Schoffa (1960). The
resulting disc of liver tissue is ground to a fine
powder in a cooled mortar with frequency additions of
liquid N₂. The liver powder is transferred to a tared
15 centrifuge tube cooled in liquid N₂ and 4 ml of ice-cold
6% (w/v) HClO₄ is then added to each gram of liver pow-
der with constant stirring. The resulting slurry is al-
lowed to thaw and then is homogenized in the centrifuge
tube at a low speed with a glass pestle. The homogenate
20 is kept ice-cold for 30 minutes, centrifuged, and the
resulting supernatant is brought to pH 6-7 with 20%
(w/v) KOH to precipitate the excess of HClO₄ as KClO₄.
The assays are carried out on the clear supernatant.

Preparation of Liver Aldolase

- 25 Livers of large (300-450g) rats are bled by perfusion
in situ with cold isoosmotic KCl and then homogenized
with 4 vol. of KCl. After centrifugation at 30000 x g
for 20 minutes, the supernatant is fractionated with
(NH₄)₂SO₄ as described by Leuthardt & Wolfe (1955).
30 The final precipitate is taken up in a small volume of
water (0.3 ml/g of original liver) and dialyzed against
200 vol. of water at 0C, changed every hour for 4h.
The cloudy preparation is centrifuged and 0.1ml of 0.1
M EDTA is added to every 4ml of clear supernatant. In-
35 cubation for 1h at 25 °C completely inactivated sorbitol
dehydrogenase (EC 1.1.1.14)

95

1

Table XVII

COMPOSITION OF FLUIDS

	UNITS	(1)	(2)	(3)
	m moles/L			
5	Na	136 - 145	40	40
	K	3.5 - 5.0	35	35
	Ca	2.1 - 2.6		
	free $[Ca^{2+}]$	[1.06]		
	Mg	0.75 - 1.25		
10	free $[Mg^{2+}]$	[0.53]		
	meq Cations	142.7 - 153.2	75	75
	Cl	100 - 106	47.5	29
	HCO ₃	26 - 28		26
	Pi	1 - 1.45	7.5	1.4
15	SO ₄	0.32 - 0.94		
	l-lactate	0.6 - 1.8	20 (d,l)	15.64
	pyruvate			1.56
	Lact/Pyr		(inf.)	10
	d-Beta OH butyrate			
20	Acetoacetate			
	Beta HB/acac			
	Acetate			
	Others			
	meq anions	128.7 - 139.4	75	75
25	Na/Cl	1.28- 1.45	0.84	1.36
	Glucose	3.9 - 5.6		278
	Fructose		278	
	CO ₂	0.99 - 1.39		1.5
	pH	7.35 - 7.45	-	7.4
30	m Osm	285 - 295	428	429.5

Footnotes for Table 1

(1) Indicates: Normal Human Plasma as reported in N.E.J.M. 283, 1285, (1970).

(2) Indicates: 5wt % Fructose in Electrolyte #75 (commercially available from Travenol as shown in "Facts & Comparisons" Aug.'83, p.52b).

(3) Indicates 5% Glucose in Electrolyte Solution for parenteral nutrition from this patient following our outlines of safe entry points and a normalized Na/Cl ratio and redox state. Such a solution improves Solution 2 in this table.

SUBSTITUTE SHEET

- 1 (Hers, 1956), which would otherwise react with fructose.
The final preparation, containing 35-45 mg of protein/ml,
is stored at -18°C and is found to lose only about 30%
activity in one year. In addition to aldolase activity,
5 it also contains glycerol 1-phosphate dehydrogenase (EC
1.1.1.8) activity and triose phosphate isomerase (EC
5.3.1.1) activity.

Other Aldolase Preparations

- Chilled fresh rat and rabbit tissues are homogenized
10 with 14 vol. of 1 mM-EDTA and centrifuged for 20 minutes
at 30000 x g. The supernatant obtained is used in assays
without further purification. A crystalline prepara-
tion of rabbit muscle aldolase is supplied by the
Boehringer Corp. (London) Ltd.

15 Analytical Methods

- ATP is determined by the method described by
Lamprecht & Trautschold (1963), ADP and AMP are determined
in the combined assay of Adam (1963), Pi was determined
by the method described by Berenblum & Chain (1938)
20 as modified by Martin & Doty (1949). Fructose 1-phosphate,
is determined by the method of Eggleston (1970). Fructose
1, 6-diphosphate, is measured together with total triose
phosphates in the combined assay of Bucher & Hohorst
(1963); pyruvate, phosphoenolpyruvate, 2- and 3-
25 phosphoglycerate are determined in sequence (Czok & Eckert,
1963). The references to other analytical methods are
as follows: α -glycerophosphate (Hohorst, 1963b); L-(+)-
lactate (Hohorst, 1963c); glucose 6-phosphate and fructose
6-phosphate (Hohorst, 1963c); glucose 1-phosphate
30 (Bermeyer & Klotzsch, 1963); glucose and fructose (Klotzsch
& Bergmeyer, 1963); the sum of D-glyceraldehyde and
glycerol (Pinter, Hayashi & Watson, 1967). For the
fluorimetric determination of very low concentrations of
glyceraldehyde 3-phosphate and dihydroxyacetone phosphate
35 by the method of Veech, Raijman, Dalziel & Krebs (1969),

1 a portion of the neutralized supernatant is shaken for
1 minute with Florisil (100-200 U.S. mesh) to remove
flavins and then recentrifuged before use. In livers
perfused with fructose where the concentration of
5 dihydroxyacetone phosphate is increased, it is determined
by the spectrophotometric method of Bucher & Hohorst
(1963). IMP is determined by a combination of paper
chromatographic separation (Krebs & Hems, 1953) and a
spectrophotometric assay. A portion of deproteinized
10 liver extract (0.1 or 0.2ml) is dried onto a 1cm area on
Whatman no. 1 chromatograph paper under a current of hot
air. Duplicates, with and without added IMP standards
(10 ul, 2mM solutions) on the same spot, are developed
by descending chromatography with the isobutyric acid-
15 ammonia solvent mixture described by Krebs & Hems (1953)
for 45-48h at room temperature. After drying in a
current of air, the papers are examined under u.v. light
from a Chromatolite lamp (Hanovia Ltd., Slough, Bucks,
U.K.) and absorbent areas are ringed by pencil. Average
20 distances run from the starting line are: IMP 23 cm,
ATP 27 cm, ADP 32, cm, AMP and inosine 37 cm. IMP areas,
and a blank area of similar size before the starting line,
are cut out and dropped into 4ml of 10mM potassium phos-
phate buffer, pH 7.0. After gentle mixing at intervals
25 for 1h, 3ml is removed and the extinction at 248nm in
1cm wide silica cells in a Zeiss spectrophotometer is
determined. At this wavelength, the $E_{\text{max}} \times 10^3$
for IMP is 12.3 (Deutsch, 1952). Recovery of
standards by the whole procedure is 93-104%.

30

RESULTS

The values of metabolites found in freeze clamped
liver are given in Table XVIII. Infusion of a fructose
solution at a rate sufficient to raise the blood fruc-
tose level to 10mM

35

SUBSTITUTE SHEET

1

TABLE XVIII

Liver Contents of Metabolites
(After 10 Minutes of Perfusion)

Values Are In uMoles/g Wet Weight

5

	(1)	(2)	(3)
D-Glucose	6.99	2.29	10
D-Fructose	about 0	10	about 0
Glucose 6-P	0.25	0.14	0.30
Fru-tose 1-P	0.23	8.72	0.25
10 Dihydroxyacetone -P	0.04	0.16	0.04
3 Phosphoglycerate	0.26	0.16	0.26
Lactate	0.79	1.34	0.79
Pyruvate	0.08	0.15	0.08

15

Footnotes for Table XVIII

(1) Indicates liver before perfusion.

(2) Indicates perfusion with solution 1 from
commercial sources.

(3) Indicates perfusion with solution 2 from this
patient.

20

- 1 drops liver and hence blood glucose level to 2.29mM
and raises fructose 1, P, over 35 fold to 8.7 umoles/g.
In contrast, using a glucose solution so as to raise the
blood level to 10 mM glucose has no appreciable
5 effects except for a small elevation of glucose 6-P.

In Table XIX, we see that raising blood
fructose causes a three fold drop in ATP and a seven
fold increase in IMP. The phosphate is simply stripped
off the nucleotides to put on fructose 1-P. In addition,
10 the inorganic Pi in liver drops from 4.2 to 1.7 umoles/g
weight. Taken together, this is a picture of profound
metabolic disorder in intracellular energy metabolism
which may be avoided by using the alternative NaCl bal-
anced, redox-balanced solution which uses nutrients of
15 the "safe entry point class".

100

Table XIX

1

Liver Content of Nucleotides and Pi

Values are in umoles/g wet weight

5		Control	Fructose	Glucose
			Solution	Solution
10			(1)	(2)
	ATP	2.22	0.51	2.22
	ADP	0.78	0.66	0.78
	AMP	0.26	0.20	0.26
	IMP	0.165	1.14	0.165
	Pi	4.25	1.67	4.25
	metabolically			
	active Pi	13.75	13.88	13.80

15

SUBSTITUTE SHEET

1 In Table XX, we see the $[NAD^+]/[NADH]$ ratio
 calculated from the $[l\text{-lactate}]/[pyruvate]$ ratio or the
 $[malate]/[oxaloacetate]$ ratio increases with fructose
 by two fold. As predicted by the equation of the K_{G+G}
 5 reaction, this is accompanied by an incredible elevation
 of the free $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$ ratio to $150,000M^{-1}$,
 the highest values ever recorded. Whether near-
 equilibrium is reached in such an abnormal situation
 is not the point here. Rather, it is clear fructose
 10 abnormally decreases not only the total amounts of the
 adenine nucleotides (Table XIX) but also severely dis-
 torts their thermodynamic relationship thereby profoundly
 disordering the normal metabolic state of liver. In
 contrast, solution 2 has no effect, firstly because it
 15 does not violate the "safe entry point" concept, and also,
 because it has pH, redox and NaCl balance.

TABLE XX

Example 2: Using Class 1 Solutions for Parenteral Nutrition
 Liver Nucleotide Ratios

	Control Liver	Liver Perfused with Parenteral Nutrient (1)	Liver Perfused with Parenteral Nutrient (2)
Free Cytoplasmic			
25 $\frac{[NAD^+]}{[NADH]}$	912	1812	912
Free Cytoplasmic*			
30 $\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]} M^{-1}$	11,517	151,000	11,517

*The free cytoplasmic $\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]}$ is calculated
 from equation 5 in this disclosure as described by Veech
 R. L., et al, J. Biol. Chem. 254, 6538-6547, 1979.

1 The example also illustrates the concept of "safe
entry points" discussed herein: Compounds which may be
included in solutions which directly contact living
cells, without, for instance, first passing through
5 the gut wall to be metabolically changed, constitute
the group herein identified by having "safe entry points".
Members of the "safe entry point group" where levels over
3mM may be used in fluids directly contacting cells
are:

10 l-Lactate
 pyruvate

d B-Hydroxybutyrate
 acetoacetate

 D-Glucose

15 The upper limits to which even these may be used
depends upon the metabolite and medical situation and
no upper limit can be set absolutely without such
considerations. However, the sum of
20 lactate and pyruvate is generally in the level of 10-
12 mM in healthy, jogging adults. The sum of
betahydroxybutyrate and acetoacetate is in the range
5-7 mM/L plasma in healthy individuals undergoing
reducing three day fasts. (See Cahill G. F. and Aoki
25 T.T. in Cerebral Metabolism and Neural Function (1980)
Passonneau J.V., Hawkins R.A., Lust W.D. and Welsh F.A.
eds; pp 234-242, Williams & Wilkins, Baltimore).
Such levels may therefore be considered to be in a
"Normal" range and used safely in most normal condi-
30 tions excepting perhaps ketones in pregnant women
where the decision by the physician will depend upon
the medical necessity. (See Rudolf M.C.J. and
Sherwin R.S., Clinics in Endocr. & Metab. 12, pp 413-
428, 1983).

35

1 The toxicity of elevating blood glucose above
13 mM/l is well documented in the studies of the
University Diabetes Group and must be balanced in
the physician's judgment by the need for calories in
5 the patient. Glucose is herein demonstrated, however,
to be much less toxic than fructose.

Compounds which may not be used parenterally as
"safe entry points" into the metabolic sequence,
as currently practiced in the art, are:

10

Acetate

Glycerol

Lactate (without pyruvate)

Pyruvate (without lactate)

15

Fructose

The methods used in this example are found in the
following reference: Woods HF, Eggleston LV, Krebs HA.
The cause of the accumulation of fructose 1-P on
fructose loading. Biochem J. 119: 501-510, 1970.

20

Example 44

Use of Class II Solutions for Peritoneal Dialysis

The procedure used here is similar to that utilized by Klim and Williamson in Biochem. J. (1982) 214, 459-464

Materials

Male Wistar rats weighing 213+35g (66), at time of death, are used: there are no significant differences between the mean body weights of the experimental groups. They are maintained on a standard small animal diet, and water ad libitum in an animal house with lights on from 08:00 to 20:00h. Chronic uremia is induced by the five-sixths bilateral nephrectomy technique (Morrison, 1966). Uremic rats are allowed approximately 14 days to recover from the last operation before use.

Peritoneal-Dialysis Solutions

A commercial peritoneal dialysis solution is used, containing 45 mM acetate and 1.5% glucose (83mM) and compared to a new dialysis solution of the present invention (Example 3). The composition of the two solutions is comparatively shown in Table XXI. Control rats are simply given glucose to raise their blood levels to those occurring in dialyzed animals.

The methods of measurement of liver metabolites are those of Veech and are described amply in the literature such as Veech et al. J. Biol. Chem. 254 6538-6547, 1979; Veech, Eggleston & Krebs Biochem. J. 115, 609-619, 1969 and Veech et al. FEBS Letts., 117, K65-72, 1980.

1

TABLE XXI

Composition of Dialysis Fluids

	Units	Normal	Commercial	New
	<u>m moles</u>	Plasma	Fluid	Fluid
5	L Fluid	(1)	(2)	(3)
	Na	136 - 145	140	140
	K	3.5- 5.0	4	4
	Ca	2.1- 2.6	2.0	2.0
	free [Ca ²⁺]	[1.06]		
10	Mg	0.75- 1.25	0.75	0.75
	Sigma mEq.Cations	142.7 - 153.2	150	150
	Cl	100 - 106	105	105
	HCO ₃	26 - 28		29
	Sigma Pi	1 - 1.45		
15	SO ₄	0.32- 0.94		
	L-lactate	0.6 - 1.8		8.21
	pyruvate			1.79
	Lact/pyr			4.6
	D-Beta-OH butyrate			3.24
20	Acetoacetate			2.76
	BetaHB/acac			1.17
	Acetate		45	
	Sigma mEq anions	128.7 - 139.4	150	150
	Na/Cl	1.28- 1.45	1.33	1.33
25	Glucose	3.9 - 5.6	83	83
	CO ₂	0.99- 1.39		1.5
	pH	7.35- 7.45	5.5-6.5	7.4
	Sigma m Osm	285 - 295	379.75	379.75

30 Footnotes for Table 1

(1) indicates: Normal plasma N.E.J.M. 283, 1285, 1970.

(2) indicates: Commercial Fluid-Peritoneal dialysis with 1.5% Glucose. American McGaw, Facts and

35 Comparisons, October 1982, page 704.

1 (3) indicates: New fluid-improved peritoneal
dialysis fluid formulated in this disclosure is meant to
mimic the ideal commercial fluid. This new fluid is not
to be taken as "ideal" but is simply a way of illustrating
5 why acetate should not be used. A better fluid would
also contain $\text{HCO}_3^-/\text{CO}_2$, Lactate/pyr & Beta-HB-/AcAc
but would have an increased Na:Cl ratio of between
1.38 to 1.41 to increase alkali reserve in the chronically
acidotic uremics. Cl^- could be 100, HCO_3^- of 34 with
10 $[\text{CO}_2]$ of 1.7mM as an example of a fluid designed in
conformity with the principles outlined herein. Such
fluids have 1) redox balance and hence normal phosphoryla-
tion state achieved with 2) pair of ratioed couples so as
to achieve a normal M desired NaCl ratio 3) while causing
15 less pathological consequences than present art allows.

1 The values of metabolites in rat liver are given
after seventy minutes of peritoneal dialysis in
Table XXII.

(Electrolyte 14)

5 Table XXII

	Control	(1) Acetate Peritoneal Dialysis	(2) Redox-Balanced Dialysis Fluid
10 N	(13)	(10)	(10)
Values are given in n moles/ g wet weight liver.			
Dihydroxy-	46	53	69
acetone P	+ ₃	+ ₅	
15 3-Phospho-	294	405	294
glycerate	+ ₁₅	+ ₂₇	
1-Lactate	727	743	6081
	+ ₃₆	+ ₇₀	
20 Pyruvate	158	98	1326
	+ ₁₃	+ ₉	
d-Beta Hydroxy-	117	151	2400
25 butyrate	+ ₂₀	+ ₁₂	
Acetoacetate	100	117	1380
	+ ₁₉	+ ₈	
30 Acetate	20	33000	20

In Table XXIII are given the changes in liver
content of divalent cations, Pi, PPi and total
metabolizable phosphate containing compounds after
such treatment.

35

1

TABLE XXIII

Changes in Mg, Ca, Pi and PPI Content in Rat Liver During
Dialysis

Values in umoles/g wet weight liver.

5

10

15

20

25

	(1)			(2)	
	Acetate	Change	New	Change	
	Dialysis	Induced	Dialysis	Induced	
		by Acetate		by new	
Control		Dialysis		Dialysis	
(16)	(16)				
Ca	1.06	1.76	+ .70	1.06	0
Mg	11.76	12.94	+1.18	11.8	0
Inorganic Pyrophosphate					
(PPi)	.018	0.198	+0.18	0.018	0
Sigma Adenine					
Nucleotides	7.95	9.43	+1.48	7.95	0
Sigma Guanine					
Nucleotides	1.56	1.97	+0.41	1.56	0
Sigma Glycolytic					
Pi	0.65	1.65	+0.06	0.85	+ .2
Sigma Metabolic					
Pi	13.75	17.97	+4.22	13.95	+ .2
from all					
measured					
Metabolites					

30

35

It should be remembered that normal hemodialysis with 35 mM acetate makes the abnormal elevation in PPI reach 100 times normal with a quadrupling of liver Ca at the expense of bone stores of calcium. It is thus exaggerated in every way. Solutions containing 35mM Na Acetate currently account for about of 80% of hemodialysis in the U.S. The increased Pi demonstrated herein during acetate dialysis is "hidden" in liver and flows out (into blood) after dialysis accounting for why such patients remain persistently hyperphosphotemic leading to much current pathology found in chronic dialysis patients.

1 The data presented in Table XXIII clearly show
that peritoneal dialysis, with acetate containing
fluids, leads to gross elevations of liver inorganic
pyrophosphate and liver calcium. While not widely
5 appreciated, inorganic pyrophosphate (PPi) is an impor-
tant controller of cellular metabolic pathways of many
types. See Lawson J.W.R. et al. in Gluconeogenesis,
1976 (Hanson R.W. & Mehlman M.A. Eds) pp 481-511, John
Wiley & Sons, New York). Changes in PPi are therefore
10 likely to be of widespread significance. The 70%
increase in liver calcium is, of course, clearly large
and of potential significance because of the importance
calcium plays as an activator of many intracellular
protein kinases.

15 Finally, Table XXIII shows that acetate induces
a rapid increase of 4.2 umoles/g wet weight of the
liver's rapidly metabolizing phosphate compounds. It
derives this excess Σ Pi from the blood and other phos-
phate stores. When the acetate is finally metabolized,
20 this phosphate returns to the blood where Pi is 1-1.45mM.
Since liver and blood are roughly equal in weight in
the normal adult, this movement of Σ Pi out of liver
must inevitably lead to the hyperphosphatemia which
is a major and persistent pathological sequelae of uremia
25 treated by current dialysis practice. This persistent
elevation of bloodPi leads to chronic hyperparathyroidism,
hypocalcemia, accelerated bone disease, ectopic calci-
fication of tissue and many other causes of morbidity
and even mortality in chronic renal disease. Because
30 the phosphate accumulates in the liver during acetate
dialysis, it is effectively "hidden" from the beneficial
effects which dialysis is trying to obtain, namely the
removal of excess dietary Σ Pi which is taken in by the
patient during the intradialysis periods.

35

1

(Electrolyte-14)

TABLE XXIV

Table XXIV gives the results obtained for the redox and phosphorylation states calculated, as described in Equations 4 and 5. Values are given as means + S.E.M.

		(1)	(2)
	Control	Acetate	New
		Dialysis	Dialysis
10	N	(5)	(6)
	Cytoplasmic free		
	$\frac{[NAD^+]}{[NADH]}$	1209*	about 1944
		+ 88	
	Mitochondrial free		
15	$\frac{[NAD^+]}{[NADH]}$	17.4	about 18.2
		+2.6	
	cytoplasmic		
	$\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]} M^{-1}$	13,700*	about 25,800
		+ 2,600	

20 *indicates significant difference at $P > 0.05$.

111

1 The use of acetate in a peritoneal dialysis
fluid obviously causes a significant decrease in the
free cytoplasmic $[NAD^+]/[NADH]$ and an even more profound
decrease in the cytoplasmic $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$ ratio.
5 This is so because the free $[NAD^+]/[NADH]$ ratio of cyto-
plasm is directly linked to the free cytoplasmic
 $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$ by equation 5. (See Veech, et al.
J. Biol. Chem. 254, 6538-6547, 1979). On page 704 of
Facts and Comparisons, October, 1982, are listed 16
10 peritoneal dialysis solutions, using 35 to 45 mMolar
(d,l)-lactate in commercial peritoneal dialysis solutions
made by four different commercial manufacturers. These
solutions, in addition to the 7 commercial acetates
containing peritoneal dialysis solutions, make up the
15 current state of the art. None achieve the normal
Na/Cl ratio they desire in the manner described herein.

No example of the effects of using 35 to 45 mM L-
lactate alone, in a peritoneal dialysis solution, need
be given. It is by now obvious, from the teachings
20 here presented, that such solutions are entirely without
redox balance but indeed induce a profound lactic acidosis
with a pathological decrease in the free cytoplasmic
 $[NAD^+]/[NADH]$ and the free cytoplasmic $[ATP]/[ADP][Pi]$
to which it is linked by equation 5. It is also obvious
25 that redox-balanced solutions, made by the principles
outlined here, would be an advance in the present art.

30

SUBSTITUTE SHEET

1

Example 45

Hemodialysis

Using hemodialysis equipment, which is the current major type in use, (see Keshaviah et al., CRC Critical Reviews in Biomedical Engineering 9, 201-244, 1983) and using the most common type of dialysis fluid currently in use in the art, which uses between 35 to 45 mMoles/L of Na acetate to correct the anion gap, (see Parsons F.M. & Stewart W.K., The Composition of Dialysis Fluid in Replacement of Renal Function by Dialysis, 2nd edition (1983) (Drukker W., Parsons F.M. & Maher J.F., eds) pp 148-170, (Martinus, Nijhoff, Hingham) we may obviously predict the effects, upon body organs such as the liver, of such treatment.

15 Methods

Rats are made uremic as described in the previous example. After five days, they are fasted, attached to a miniature hemodialysis apparatus, heparinized and dialyzed with two different solutions, one representing the most common types of currently used hemodialysis solutions, and another where the anion gap is made up without the use of $\text{HCO}_3^-/\text{CO}_2$, but instead, with the use of L-lactate/pyruvate and D-B-Hydroxybutyrate/acetoacetate as are given in the class 2-a solutions in this disclosure, as for example 2-a-8, Redox-Balanced Ringers. It should be understood that I do not conclude such a solution as 2-a-8 is the best solution for such a purpose, but I shall show it is superior to the existing art and may be used in the bulk of existing apparatus which contain deaerators* and currently use acetate containing hemodialysis fluids. (Keshaviah et al. CRC Critical Reviews in Biomedical Engineering 9, 201-244, 1983). A few current machine, typically 1 out of 10 in the dialysis centers I have surveyed have dialysis machines of the type described by

- 1 Miller J.H. et al. Trans Am Soc artif Internal Organs 25,
404-408, 1979. Such machines can use HCO_3^- containing
solutions. Such $\text{HCO}_3^-/\text{CO}_2$ solutions are preferred.

The compositions of the two example solutions

- 5 are given in Table XXV.

Example 4 Table XV Solution for Hemodialysis of a Uremic Rat.

Units	Normal Plasma M.E.J.M. 283, 1285 1970	(1) Usual Hemo- dialysis Solution	(2) Redox- Balanced Hemodialysis Solution
Na	136 - 145	130-135	130
K	3.5 - 5.0	0 - 1.5	4
Ca free (Ca ²⁺) [1.06]	2.1 - 2.6	1.25	1.5
Mg free (Mg ²⁺) [0.53]	0.75 - 1.25	0.5	-
2mEq Cations	142.7-153.2	133.5-140	137
Cl	100 - 106	100.5	96
HCO ₃	26 - 28		
Σ Pi	1 - 1.45		
SO ₄	0.32 - 0.94		
L - lactate	0.6 - 1.8		32.1
pyruvate			1.9
Lact/pyr			17

SUBSTITUTE SHEET

114a

D B OHbutyrate	5
acetoacetate	2
B HB/ acac	2.5
acetate	33.5-40
Other	
Σ mEq anions 128.7-139.4	137
la/Cl	1.28 - 1.45 1.29-1.34
Glucose	3.9 - 5.6 0-101
or others	
CO ₂	0.99 - 1.39 0
pH	7.35 - 7.45 ~6.5
Σ mOsm	285 - 295 270.25 to 375
	272.5

(1) The composition of the usual hemodialysis solution is taken from Parson's and Stewart, 1983, cited above.

(2) Composition of solution 2-a-8 is taken from this application except that the lactate/pyruvate ratio is decreased to 17 to approximate the absence of glucose since most current hemodialysis fluids use acetate without glucose. This composition is chosen to compare with current acetate hemodialysis practice. This solution should not be taken as "ideal" or even as recommended, but rather illustrative.

SUBSTITUTE SHEET

115

1 The rats are dialyzed with solutions 1 and 2
for four hours; the animals are sacrificed and the livers
freeze clamped. A group of normal rats, starved 48 hours,
are also sacrificed and their livers freeze clamped
5 to serve as controls. Metabolites are measured, as
previously described.

 In Table XXVI, we see that both acetate and new
redox-balanced dialysis fluids elevate liver sugar and
the first portion of the gluconeogenic pathway. During
10 acetate dialysis, changes occur throughout the glucone-
ogenic sequence and the ratio of one metabolite to
another changes.

15

SUBSTITUTE SHEET

1 Table XXVI Liver Metabolites from Rats Dialysed with Acetate
 Dialysis Fluid versus New Redox-Balanced Dialysis
 Fluids without $\text{HCO}_3^-/\text{CO}_2$
 Values are given as means + S.E.M. in nmoles/g wet
 5 weight. A * indicates a significant difference
 from normal rats at $P < 0.05$ as judged by Student's T
 Test

		Untreated Starved Rats	Commercial Acetate Dialysis	New Redox-Balanced Dialysis
10	N	13	10	
	10^{-3} x glucose	4.81+0.21	7.94+0.42	7.2*
	glucose 6-P	59+2	99*+10	88.5*
	glucose 1-P	7+1	11*+1	10.5*
	fructose 6-P	17+1	32*+3	25.2*
15	fructose 1,6 bis-P	4.6+0.4	23*+6	6.9
	DHAP	11+1	36*+4	16.5
	3-phosphoglycerate	156+14	581*+62	234
	PEP	73+5	330*+40	110
	pyruvate	10+1	27*+6	1260*
20	L-lactate	171+17	721+208	21300*
	L-malate	268+28	592*+84	402
	α -ketoglutarate	118+13	86+17	177
	isocitrate	17+2	41*+3	25.5
	citrate	308+42	944*+85	462
25	acetoacetate	638+33	643+66	1330*
	D-B OHbutyrate	1643+75	983*+83	3300*
	UDP-glucose	350+15	367+25	350
	UTP	205+9	186+8	205
	acetate	20	25000	20
30				

- 1 In Table XXVII are presented the changes in the
controlling co-factor ratios after the two types of
dialysis.

TABLE XXVII

5 Free Nucleotide Ratios in Freeze Clamped Rat Liver After
Acetate and Redox-Balanced Hemodialysis

Values are given as mean + S.E.M. An * indicates
a significant difference from control values of
 $P < 0.02$ as judged.

10	Starved Control (n) (13)	Acetate Dialysis (10)	Redox-Balanced Dialysis
	Cytoplasmic		
	$\frac{[NAD^+]}{[NADH]}$		
15	587 + 86	391 + 35	587
	$10^3 \times \frac{[NADP^+]}{[NADPH]}$		
	7.3 + .7	2.1* + .3	7.3
20	$\frac{[\sum ATP]}{[\sum ADP][\sum Pi]M^{-1}}$	3710 + 580	2090 + 280
	mitochondrial		
	$\frac{[NAD^+]}{[NADH]}$		
	8.1 + 0.7	13.8* + 1.4	8.1

- 25 In Table XXVII we see that acetate dialysis causes
oxidation of the mitochondrial $[NAD^+]/[NADH]$ ratio and
reduction of the free cytoplasmic $[NADP^+]/[NADPH]$ ratio
while redox-balanced dialysis causes no change as judged
by the isocitrate/ α -ketoglutarate ratio.

30

35

SUBSTITUTE SHEET

1 In Table XXVIII are presented the results of
the measurement of the Ca, Mg, phosphate and pyro-
phosphate content of rat liver after acetate versus redox-
balanced hemodialysis.

5 TABLE XXVIII
Changes in Mg, Ca and Phosphate Compounds in
Liver Following Acetate versus Redox-Balanced
Hemodialysis.

		Control	Acetate Hemodialysis	Redox-Balanced Hemodialysis
10	n	13	10	
	Ca	1.33	+2.89	0
	Mg	10.1	+1.8	0
	PPi	0.024	+2.00	0
15	Pi	4.22	+3.73	0
	Σ Adenine Nucleotide			
	Pi	9.32	+0.07	0
	Σ Guanine Nucleotide			
	Pi	1.76	+0.19	0
20	Σ Glycolytic Pi	0.36	+0.86	+0.50
	Σ Pi Increased from			
	All measured			
	metabolites	15.71	+8.85	+0.50

25 We see in Table XXVIII that acetate dialysis
raises inorganic pyrophosphate 200 times while redox-
balanced dialysis makes no change. Acetate hemodialysis
increases liver calcium three fold; redox-balanced
dialysis makes no change. Acetate hemodialysis increases
30 total liver metabolizable phosphate by 8.8 m moles/g,
while redox-balanced dialysis increases liver
metabolizable phosphate by only 0.5 m moles/g, or 16 times.
The "hidden" phosphate, inaccessible to dialysis after
acetate hemodialysis, is the largest ever seen. The
35 metabolic pathology is therefore even greater than that
in Example 44.

Example 45

1 Solutions of this invention when administered
not only regulate redox state and phosphorylation,
but also further tend to normalize the following
states:

- 5 (1) Distribution of water between intracellular
and extracellular fluid.
- (2) Distribution of the inorganic electrolytes
Na⁺, K⁺, Cl⁻ and Ca²⁺ between intracellular
and extracellular fluid, and
- 10 (3) Transmembrane cellular potential. ΔE

The following equations state the governing
scientific laws involved:

0. Eqn 0 - The Second Law

J. Willard Gibbs. On the equilibrium of heterogeneous substances. *J Conn Acad Sci* 1876: III: 343.

0 - 1 Definition of Gibbs Free Energy and Other Properties of State:

$$G = H - TS$$

where:

G ~ Gibbs free energy
H ~ Enthalpy or heat content
T ~ absolute temperature
S ~ Entropy, or state of randomness or disorder

0 - 1 a Entropy may be more rigorously defined by statistical and quantum mechanics in the Boltzmann Equation:

$$S = k_B \ln \Omega$$

where:

S ~ Entropy
k_B ~ Boltzmann constant = $\frac{R \text{ (gas constant)}}{\text{Avagadro's number}}$

$$\Omega \sim \text{Degeneracy} = 1.38 \times 10^{-23} \text{ J/K}$$

$$\Delta G = \Delta H - T \Delta S$$

where ~ change in

0 - 2

SUBSTITUTE SHEET

120a

0 - 3 Standard Free Energy $\sim \Delta G^0$

$$\Delta G = \Delta G^0 + RT \ln \frac{[\text{products}]}{[\text{reactants}]}$$

where:

$$R \sim \text{gas constant} \\ = 1.987 \text{ calories/}^{\circ}\text{K/mole}$$

$$T = \text{and } ^{\circ}\text{K} \sim 273 + ^{\circ}\text{C} \\ \ln \sim 2.303 \log_{10}$$

$$0 - 3a \quad \Delta G^0 = - RT \ln K_{eq}$$

where:

$$K_{eq} \sim \frac{[\text{products}]}{[\text{reactants}]}$$

0 - 4 At equilibrium, $\Delta G = 0$, so in $A + B \leftrightarrow C + D$

$$\Delta G = - RT \ln K_{eq} + RT \ln \frac{[C][D]}{[A][B]}$$

where:

$$[] \sim \text{activity or } \sim \text{concentration}$$

"A theory is the more impressive the greater the simplicity of its premises, the more different are the kinds of things it relate, and the more extended is its range of applicability... It is the only physical theory of universal content which I am convinced, that within the framework of applicability of its basic concepts, will never be overthrown.

A. Einstein

SUBSTITUTE SHEET

121

1 I Egn 1 - The Henderson-Hasselbalch Equation

The major buffer and controller of extra and intracellular pH.

Henderson LJ. Blood, A study in General Physiology.

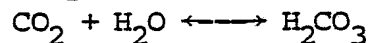
5 Silliman Lectures, Yale University Press, 1928

$$1.a \quad pH = pK_a + \log \frac{[HCO_3^-]}{[CO_2]}$$

where:

10 $pK_a = 6.10$ at $38^\circ C$ and serum concentrations of electrolytes

1.b The solubility of CO_2 in fluid, i.e. dissolved CO_2 gas plus H_2CO_3 from:



$$15 \quad [CO_2] \text{ in mmol/liter} = \frac{pCO_2 \text{ in mmHg}}{760 \text{ mmHg}} \cdot \frac{\text{cmL } CO_2/\text{mL of } H_2O}{22.26 \text{ L/mole}} \cdot \frac{1000 \text{ mmol}}{\text{mole}}$$

$\alpha_{CO_2} = 0.553/\text{mL serum } H_2O$ at $38^\circ C$ from:

Van Slyke DD. J Biol Chem 73: 765-799, 1928

20 1.c The pH of a bicarbonate containing solution to which has been added a carboxylic acid such as acetic, lactic, acetoacetic acid with a pK' in the 3 to 4 range and where the concentration of HCO_3^- is much larger than the concentration of carboxylic acid:

$$25 \quad pH = pK_a - \log \left\{ \frac{[HCO_3^-]}{2([HCO_3^-] - [HA])} - \frac{1}{2} \right\}$$

Thus adding 1.8 mM Hlactate and 0.2 mM Hpyruvate to 25 mM $NaHCO_3$ yields what pH?

$$30 \quad pH = pK_a - \log \left\{ \frac{[25]}{2([HCO_3^-] - [HA])} - \frac{1}{2} \right\}$$

$$= 6.1 - (1.36)$$

$$= 7.46$$

35

II Donnan Equilibrium Equation

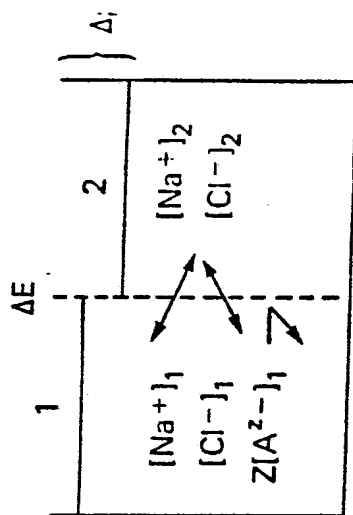
Donnan F.G.Z *Electrochem* 17: 572, 1911Donnan F.G. *Chem Rev* 1: 73-90, 1924.

1. From Gibbs (Eqn 0)

$$RT \ln \frac{[Cl^-]_1}{[Cl^-]_2} + RT \ln \frac{[Na^+]_1}{[Na^+]_2} = 0$$

Or:

$$1.a \quad \frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[Na^+]_2}{[Na^+]_1}$$



[] \approx activity \approx concentration
 A \approx non-diffusible polyanion
 Z \approx valence of polyanion

$$\text{Therefore:} \quad \frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[Cl^-]_2}{[Cl^-]_1 + Z[A^{2-}]_1} = \frac{[Na^+]_2}{[Na^+]_1}$$

and for polyvalents:

$$\left\{ \frac{[Anions]_1}{[Anions]_2} \right\}^{1/z \text{ anions}} = \left\{ \frac{[Cations]_2}{[Cations]_1} \right\}^{1/z \text{ cations}}$$

122a

2. From the Law of Electrically Neutrality:

$$[\text{Na}^+]_2 = [\text{Cl}^-]_2$$

$$[\text{Na}^+]_1 = [\text{Cl}^-]_1 + 2 [\text{A}^{2-}]_1$$

3. Quadratic equation:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Example:

Consider albumin dialysed against 100% CO_2 / 3.13 NaHCO_3 buffer with 1.17 mM albumin (i.e. 8% solution). Hypothetically keep charge on albumin at -20/mole.

$$\begin{aligned} \frac{[\text{HCO}_3^-]_i}{[\text{HCO}_3^-]_o} &= \frac{[\text{HCO}_3^-]_o}{[\text{HCO}_3^-]_i + 20[\text{Alb}^{20-}]} = \frac{[\text{Na}^+]_o}{[\text{Na}^+]_i} \\ \frac{[\text{HCO}_3^-]_i}{[3.13 \times 10^{-3}]} &= \frac{[3.13 \times 10^{-3}]}{[3.13 \times 10^{-3}] + 20[1.17 \times 10^{-3}]} \\ [\text{HCO}_3^-]_i &= 0.4 \times 10^{-3} \text{M} \end{aligned}$$

II Eqn 2 Multicomponent Donnan Equilibrium System for Solutions Such as the Hemodialysis of Blood Plasma Electrolytes:

where $\Delta p = 0$ and all components but albumin are permeant. Subscript $_0$ ~ in dialysis fluid, subscript $_i$ ~ in patient's plasma, Δp ~ difference in pressure.

$$2.a. \quad \frac{[Na^+]_i}{[Na^+]_0} = \frac{[K^+]_i}{[K^+]_0} = \frac{[Ca^{2+}]_i}{[Ca^{2+}]_0} = \frac{[Mg^{2+}]_i}{[Mg^{2+}]_0} = \frac{[Cl^-]_i}{[Cl^-]_0} = \frac{[HCO_3^-]_i}{[HCO_3^-]_0} = \frac{[Pi]_i}{[Pi]_0} = \frac{[Lac^-]_i}{[Lac^-]_0} = \frac{[pyr^-]_i}{[pyr^-]_0} = \frac{[acet^-]_i}{[acet^-]_0} = \frac{[BHB^-]_i}{[BHB^-]_0} = \frac{[acac^-]_i}{[acac^-]_0} = \frac{[BHB^-]_i}{[BHB^-]_0} = \frac{[acet^-]_i}{[acet^-]_0}$$

Statement of electrical neutrality on two sides of an uncharged membrane

2.b.1.

$$[Na^+]_0 + [K^+]_0 + 2[Ca^{2+}]_0 + 2[Mg^{2+}]_0 = [Cl^-]_0 + [HCO_3^-]_0 + 1.8[Pi^{-1.8}]_0 + [Lac^-]_0 + [pyr^-]_0 + [acac^-]_0 + [BHB^-]_0 + [acet^-]_0$$

2.b.2.

$$[Na^+]_i + [K^+]_i + 2[Ca^{2+}]_i + 2[Mg^{2+}]_i = [Cl^-]_i + [HCO_3^-]_i + 1.8[Pi^{-1.8}]_i + [Lac^-]_i + [pyr^-]_i + [acac^-]_i + [BHB^-]_i + [acet^-]_i + Z[prot^{2-}]_i$$

Distribution of cations on two sides of the membrane:

2.c

$$[K^+]_i = [K^+]_0 \frac{[Na^+]_i}{[Na^+]_0}; [Ca^{2+}]_i = [Ca^{2+}]_0 \left(\frac{[Na^+]_i}{[Na^+]_0} \right)^2; [Mg^{2+}]_i = [Mg^{2+}]_0 \left(\frac{[Na^+]_i}{[Na^+]_0} \right)^2$$

Distribution of Anions:

123a

2.d

$$[Cl^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [Cl^-]_0; [HCO_3^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [HCO_3^-]_0; [acet^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [acet^-]_0; [Pi]_i = \frac{[Na^+]_i}{[Na^+]_0} [Pi]_0; [lact^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [lact^-]_0; [pyr^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [pyr^-]_0; [acac^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [acac^-]_0; [BHB^-]_i = \frac{[Na^+]_i}{[Na^+]_0} [BHB^-]_0$$

Now solving for $[Na^+]_i/[Na^+]_0$ for a dialysis fluid of known composition:

2.e

$$\frac{[Na^+]_i}{[Na^+]_0} [Na^+]_0 + [K^+]_0 + 2 \frac{[Na^+]_i}{[Na^+]_0} [Ca^{2+}]_0 + [Mg^{2+}]_0 =$$

$$\frac{[Na^+]_i}{[Na^+]_0} [Cl^-]_0 + [HCO_3^-]_0 + [acet^-]_0 + [lact^-]_0 + [pyr^-]_0 + [acac^-]_0 + [BHB^-]_0 + 1.8 \frac{[Na^+]_i}{[Na^+]_0} [Pi]_0 + \frac{[Na^+]_i}{[Na^+]_0} [Z]_0 + [prot^{2-}]_0$$

and:

$$\frac{[Na^+]_i}{[Na^+]_0} + [K^+]_0 + 2 \frac{[Na^+]_i}{[Na^+]_0} [Ca^{2+}]_0 + [Mg^{2+}]_0 + \frac{[Na^+]_i^2}{[Na^+]_0^2} + \frac{[Na^+]_i^3}{[Na^+]_0^3} - [Z]_0 - (1.8 [Pi]_0 + 0.8 [Na^+]_0) \frac{[Na^+]_i}{[Na^+]_0} (-0.8) =$$

$$[Cl^-]_0 + [HCO_3^-]_0 + [acet^-]_0 + [lact^-]_0 + [pyr^-]_0 + [acac^-]_0 + [BHB^-]_0$$

Plasma [concentration] ~ 0.935 x plasma H_2O [concentration]

124

1 III

Eqn 3. Nernst Equation - ΔE
 Nernst W. Theoretical Chemistry 4th Edition, 1904,
 McMillan, London. See also Silliam Lecture, 1906, Yale
 U. Press, New Haven.

5

$$3. \quad \Delta E = - \frac{RT}{nF} \ln \frac{[\text{anion}^-]_{\text{outside}}}{[\text{anion}^-]_{\text{inside}}}$$

or:

10

$$\Delta E = - \frac{RT}{nF} \ln \frac{[\text{cation}^+]_{\text{inside}}}{[\text{cation}^+]_{\text{outside}}}$$

where:

at 38°C T ~ 311 °K

R, the gas constant ~ 8.314 hyykes/degree/mole

15

n ~ number of equivilents

F, the Faraday, ~ 96,494 coulombs

 ΔE ~ potential in voltsTo convert ln to log₁₀, multiply by 2.303

20

From Cornell N, Anal Biochem 1980; 102: 326-331, for
 isolated hepatocytes from starved rats incubated in Krebs-
 Henseleit.

$$[0.128 \text{ M Cl}^-]_{\text{outside}}$$

$$\Delta E = -0.0617 \log \frac{[0.128 \text{ M Cl}^-]_{\text{outside}}}{[0.041 \text{ M Cl}^-]_{\text{inside}}}$$

$$[0.041 \text{ M Cl}^-]_{\text{inside}}$$

25

$$\Delta E = -0.0305 \text{ V or } -30.5 \text{ mV}$$

and for cat brain, from Eccles JC. The Physiology of Nerve
 Cell, 1957, Johns Hopkins U Press, Baltimore.

$$[0.125 \text{ M Cl}^-]_{\text{outside}}$$

$$\Delta E = -0.0617 \log \frac{[0.125 \text{ M Cl}^-]_{\text{outside}}}{[0.009 \text{ M Cl}^-]_{\text{inside}}}$$

30

$$[0.009 \text{ M Cl}^-]_{\text{inside}}$$

$$\Delta E = -0.0705 \text{ V or } -70.5 \text{ mV}$$

3.b Redox Potential of Half Reactions

$$\frac{RT}{nF} \frac{[\text{oxidized}]}{[\text{reduced}]}$$

$$E_h = E^{\circ} + \frac{RT}{nF} \ln \frac{[\text{oxidized}]}{[\text{reduced}]}$$

35

where:

R ~ 8.31431 J/°K/mole

T ~ °K

n ~ number of electrons

F ~ Faraday ~ 96,494 coulombs

ln ~ 2.03 log₁₀

SUBSTITUTE SHEET

IV Eqn 4 Redox State Equations. $[NAD^+]/[NADH]$ or $[NADP^+]/[NADPH]$.

Near equilibrium reactions are given a number depending upon location. The E^0 of the $[NAD^+]/[NADH]$ couple at pH 7 is -0.32V. That of the $[NADP^+]/[NADPH]$ couple, -0.335 V.

Enzyme No.	Abbreviation	Definition of K_{eq}	Value of K_{eq} at pH = 0	Value of K_{eq} at pH 7	E^0 at pH 7.0	E^0 at pH 7.0
					oxidized	reduced
					$CO_2 = 1.5 \text{ mM}$	or $0.5 \text{ mM } NH_4^+$
					V	or $1 \text{ mM } Pi$

Cytoplasmic NAD - Linked Dehydrogenases

4 c 1	K_{LDH}	$\frac{[pyruvate^-][NADH][H^+]}{[lactate^-][NAD^+]}$	$1.11 \times 10^{-11} \text{ M}$	1.11×10^{-4}	-0.201	
EC 1.1.1.27						
4 c 2	K_{MDH}	$\frac{[oxaloacetate^{2-}][NADH][H^+]}{[malate^{2-}][NAD^+]}$	$2.86 \times 10^{-12} \text{ M}$	2.86×10^{-5}	-0.184	
EC 1.1.1.37						
4 c 3	K_{GPDH}	$\frac{[\alpha\text{-glycerol-}P^{2-}][NADH][H^+]}{[DHAP^{2-}][NAD^+]}$	$1.3 \times 10^{-11} \text{ M}$	1.3×10^{-4}	-0.263	
EC 1.1.1.94						
4 c 4	K_{GAPDH}	$\frac{[1,3 \text{ DiPG}^{4-}][NADH][H^+]}{[GAP^{2-}][P_i^{2-}][NAD^+]}$	$5.3 \times 10^{-8} \text{ M}$	5.3×10^{-1}	-0.302	Here, P_i is a reactant
EC 1.2.1.12						
K_{ADH}		$\frac{[acetaldehyde][NADH][H^+]}{[ethanol][NAD^+]}$	$1.94 \times 10^{-11} \text{ M}$	1.9×10^{-4}	-0.209	
EC 1.1.1.1						
K_{IDH}		$\frac{[d\text{-fructose}][NADH][H^+]}{[d\text{-sorbitol}][NAD^+]}$	$1.14 \times 10^{-9} \text{ M}$	1.14×10^{-2}	-0.252	
EC 1.1.1.14						

125a

Mitochondrial NAD - Linked Dehydrogenases

4	1	K_{HBDH}	=	$\frac{[\text{acetoacetate}^-][\text{NADH}][\text{H}^+]}{[\text{d-B-hydroxybutyrate}^-][\text{NAD}^+]}$	$4.93 \times 10^{-9} \text{ M}$	4.93×10^{-2}	-0.261
		EC 1.1.1.30					
4	2	K_{GIDH}	=	$\frac{[\alpha\text{-KG}^{2-}][\text{NH}_4^+][\text{NADH}][\text{H}^+]}{[\text{l-glutamate}][\text{NAD}^+]}$	$3.87 \times 10^{-13.2} \text{ M}^2$	3.87×10^{-6}	-0.158
		EC 1.4.1.3					
		K_{ALDH}	=	$\frac{[\text{acetate}^-][\text{NADH}][\text{H}^+]^2}{[\text{acetaldehyde}][\text{NAD}^+]}$	$1.45 \times 10^{-5.2} \text{ M}^2$	$1.45 \times 10^{+9}$	-0.596
		EC 1.2.1.3					

Cytoplasmic NADP - Linked Dehydrogenases

4	1	K_{ICDH}	=	$\frac{[\alpha\text{-KG}^{2-}][\text{CO}_2][\text{NADPH}]}{[\text{l-isocitrate}^3-][\text{NADP}^+]}$	1.17 M	1.17 M	-0.337
		EC 1.1.1.42					
4	2	$K_{\text{Malic Enz}}$	=	$\frac{[\text{pyruvate}^-][\text{CO}_2][\text{NADPH}]}{[\text{malate}^2-][\text{NADP}^+]}$	$3.44 \times 10^{-2} \text{ M}$		-0.422
		EC 1.1.1.40					
4	3	K_{P6DH}	=	$\frac{[\text{ribulose } 5\text{-P}^{2-}][\text{CO}_2][\text{NADPH}]}{[\text{6-phosphogluconate}^3-][\text{NADP}^+]}$	$1.72 \times 10^{-1} \text{ M}$		
		EC 1.1.1.43					

* See ref.

...

Linking Isomerases

4 L 1	$K_{60T} = \frac{[\alpha\text{-KG}^{2-}][\text{l-aspartate}^-]}{[\text{l-glutamate-}][\text{oxaloacetate-}]}$	6.61
	EC 2.6.1.1	
4 L 2	$K_{8PT} = \frac{[\alpha\text{-KG}^{2-}][\text{l-alanine}]}{[\text{l-glutamate-}][\text{pyruvate-}]}$	1.52
	EC 2.6.1.2	
4 L 3	$K_{TP1} = \frac{[\text{dihydroxyacetone-P}^{2-}]}{[\text{glyceraldehyde 3-P2-}]}$	22
	EC 5.3.1.1	

References for Values of Near-Equilibrium Reactions in Equation 4

Equation	Abbreviation	Reference
4 C 1	K_{LDH}	Williamson DH, Lund P, Krebs HA. <i>Biochem J</i> 103: 514-527, 1967
4 C 2	K_{MDH}	Guyon R, Gelberg H, Veech RL. <i>J Biol Chem</i> 248: 6957-6965, 1973
4 C 3	K_{GPDH}	Russman W. <i>Thesis</i> , Munich, 1969.
4 C 4	K_{GAPDH}	Cornell N, Leadbetter H, Veech RL. <i>J Biol Chem</i> 254: 6522-6527, 1979
4 M 1	K_{HBDH}	Williamson DH, Lund P, Krebs HA. <i>Biochem J</i> 103: 514-527, 1967
4 M 2	K_{GLOH}	Engel P, Dalziel K. <i>Biochem J</i> 105: 691-695, 1967

126a

- 4 T 1 K_{ICDH} Londesborough J, Dalziel K. *Biochem J* 110: 217-222, 1968
- 4 T 2 $K_{H.E.}$ Veech R, Eggleston LV, Krebs HA. *Biochem J* 115: 609-619, 1967
- 4 T 3 K_{6PGDH} Villet R, Dalziel K. *Biochem J* 115: 633-638, 1969
- 4 L 1 K_{GOT} Krebs HA. *Adv Enz Reg* 13: 449-472, 1975
- 4 L 2 K_{GPT} Krebs HA. *Adv Enz Reg* 13: 449-472, 1975
- 4 L 3 K_{TP1} Veech RL, Rajman L, Dalziel K, Krebs HA. *Biochem J* 115: 837-842, 1969

The enzyme aldose reductase EC 1.1.1.21 may be redox active during fructose infusion in certain tissues.
The reaction is:

$$K_{Aldose R} = \frac{[d-sorbitol][NADPH][H^+]}{[d-glucose][NADP^+]} \cdot 2 \times 10^{-11} \text{ M.} \quad \text{My estimate}$$

For description, see Hayman S, Kinoshita JH. *J Biol Chem* 240: 877, 1965

INSTITUTE SHEET

V Eqn 5 Phosphorylation State Equations - $\frac{[\Sigma \text{ATP}]}{[\Sigma \text{ADP}][\Sigma \text{P}_i]}$ Veech RL, Lawson JR, Cornell NW, Krebs HA. *J Biol Chem* 254: 6538-6547, 1979

5a. The equilibrium constant of the glyceraldehyde 3-phosphate dehydrogenase (EC 1.1.1.29) and 3 phosphoglycerate kinase reactions (EC 2.7.2.3) at 38°C, $I = 0.25$, and free $[\text{Mg}^{2+}] = 1 \text{ mM}$ is:

$$K_{6+6} = \frac{[\Sigma \text{3PG}] [\Sigma \text{ATP}] [\text{NADH}][\text{H}^+]}{[\Sigma \text{6AP}] [\Sigma \text{ADP}][\Sigma \text{P}_i] [\text{NAD}^+]} = 1.83 \times 10^{-4}$$

5b. Combining the above reaction with K_{LDH} and substituting $[\text{DHAP}] = [\text{6AP}]/22$

$$K_{6+6}^{\text{LDH}} = \frac{[\Sigma \text{3PG}] [\Sigma \text{ATP}] [\text{l-lactate}]}{[\Sigma \text{6AP}] [\Sigma \text{ADP}][\Sigma \text{P}_i] [\text{pyruvate}]} = 1.65 \times 10^{-7} \text{ M}^{-1}$$

5c. Or:

$$\text{Free Cytoplasmic} \frac{[\Sigma \text{ATP}] [\Sigma \text{DHAP}] [\text{pyruvate}]}{[\Sigma \text{ADP}][\Sigma \text{P}_i] [\Sigma \text{3PG}] [\text{l-lactate}]} = \frac{1}{7.5 \times 10^{-5} \text{ M}^{-1}}$$

5d. Alternatively, from the creatine phosphokinase reaction (EC 2.7.3.2)

127a

$$K_{CK} = \frac{[ATP] [creatine]}{[ADP] [creatine-P][H^+]} = 1.6 \times 10^{-9} - 1$$

For the Pyrophosphorylation State or [P Pi]/[Pi]:

Lawson JMR, Guynn RW, Cornell MW, Veech RL. In *Gluconeogenesis* (Hanson RW, Mehler MA eds) pp 461-511, John Wiley, New York, 1976

Se. From the UDP6 Pyrophosphorylase reaction (EC 2.7.7.9):

$$\text{Free Cytoplasmic } [P Pi] = \frac{[glucose 1-P][UTP]}{[UDPglucose] K_{UDP6Pylase}}$$

$$\text{where } K_{UDP6Pylase} = 4.55$$

Sl. For liver and blood glucose:

$$K_{6-P-Pi \text{ Trans Pase}} = \frac{[6glucose 6-P][xPi]}{[Glucose][xPPi]} = 45.9$$

5g.

$$K_{6-P-Pi \text{ Trans Pase}} = \frac{[free F 1,6 diP][xPi]}{[xfructose 6-P][xPPi]} = 29.0$$

VI Eqn 6 Determination of Osmotic Pressure - π Van't Hoff JH. *Arch Neerl Sci* 20: 239-303, 1886

$$\pi = \sum [C] RT$$

where:

- π ~ osmotic pressure in atmospheres (relative to pure H₂O)
- $\sum [C]$ ~ [concentrations] of solutes in mole/liter
- R ~ gas constant = 0.082 liter atmospheres/
mole/ degree K
- T ~ 273 + °C

VII Eqn 7 The Equation of State of the Cell

Relating the E across the cell membrane, the distribution of $[Na^+]$, $[K^+]$, $[Cl^-]$, and $[Ca^{2+}]$ between extracellular fluid and cytoplasmic H_2O and hence cell volume to the cytoplasmic $[ATP]/[ADP][P_i]$

$$\Delta G_{Na/K \text{ ATPase}} = \Delta G_{ATPase} + \Delta G_{ions} + RT \ln \frac{[ADP][P_i]}{[ATP]} + RT \ln \frac{[Na^+]_o^3 [K^+]_i^2 [Cl^-]_o}{[Na^+]_i^3 [K^+]_o^2 [Cl^-]_i} + TS$$

Since $\Delta G = 0$, then:

$$0 = -7.73 \text{ kcal/mole} + 0 + (-6.3 \text{ kcal/mole}) + 8.5 \text{ kcal/mole} + 5.5 \text{ kcal/mole}$$

$$\text{As } 1 \text{ kcal/mole} = \frac{0.082 \text{ liter atmos/mole/}^\circ\text{K}}{1.98 \times 10^{-3} \text{ kcal/mole/}^\circ\text{K}} \times \frac{1}{22.4 \text{ l/mole}} = 1.85 \text{ atmospheres}$$

then the TS term = $5.5 \times 1.85 = 10.2 \text{ atmospheres}$.

And further from Van't Hoff (Eqn 6)

$$\Sigma [C]_{in} - \Sigma [C]_{out} = \frac{\Delta G}{RT}$$

$$\Sigma [C]_{in} - \Sigma [C]_{out} = 0.40 \text{ moles/L}$$

Eqn 7 states that since ΔG H₂O outside = ΔG H₂O inside, the cell is prevented from swelling by the Na⁺/K⁺ ATPase which electroreutrally pumps out 2 mOsmoles/ ATP hydrolysed. The ΔE across the cell (membrane) is reflected by the distribution of $[Cl^-]_o / [Cl^-]_i$ in accordance with the Nernst equation (Eqn 3). The TΔS or decreased entropy within the living cell represents the increase "order" characteristic of the living cell. See Eqn 0.

1 7b. From the high capacity $\text{Na}^+/\text{Ca}^{2+}$ exchanger written in
 an electroneutral manner reflecting the free permeability
 of Cl^- in accordance with the dictates of the Nernst
 equation, (Eqn 3):

5 $3 \text{Na}^+_o + \text{Ca}^{2+}_i + \text{Cl}^-_o \leftarrow \rightarrow 3 \text{Na}^+_i + \text{Ca}^{2+}_o + \text{Cl}^-_i;$
 The net osmolar movement of eqn 7a is 2 osmoles \rightarrow
 outside. In contrast, the net movement of eqn 7b is 3
 osmoles \rightarrow inside, requiring the Na^+/K^+ ATPase to cycle
 3 times for each 2 times the $\text{Na}^+/\text{Ca}^{2+}$ exchange mechanism
 10 operates in order to maintain osmotic equilibrium.

The gradient $[\text{Ca}^{2+}]_i / [\text{Ca}^{2+}]_o$ is thus a direct
 function of the $[\text{Na}^+]_o^3 / [\text{Na}^+]_i^3$, (the $[\text{Cl}^-]_o / [\text{Cl}^-]_i$),
 and a function of the phosphorylation and entropy state
 of the cell.

15

1 It will be clear to those skilled in the art
that equation 7 is the statement of the reaction which
links the external environment of the cell to its
internal environment and metabolic machinery.

5 Extracellular fluid is thus a creation of the metabolic
process of the cell. Changing the external $[Na^+]$,
 $[K^+]$, $[Cl^-]$, or $[Ca^{2+}]$, or the $[H_2O]$ must necessarily
effect the same parameters inside the cell.

 Additionally, the redox and phosphorylation
10 states, the ΔE , and the $T\Delta S$ of the cell are all
related and therefore manipulable by the relationships
given.

 To control these parameters one needs to use
solutions as provided herein which include defined
15 concentrations of Na^+ , K^+ , Cl^- and Ca^{++} and the
related ions HCO_3^- , H^+ , at a defined Mg^{2+} concentration
and with a defined osmotic pressure.

 Thus, the present invention provides a process
for regulating:

- 20 1) Distribution of water between intracellular
and extracellular fluid.
 2) Distribution of the inorganic electrolytes
 Na , K , Cl and Ca between intracellular
and extracellular fluid.
25 3) and transmembrane cellular potential

 This process is practiced by contacting cells with
aqueous near-equilibrium couples as taught by this
inventor or by varying the external concentration of
 Na^+ , K^+ , Cl^- or Ca^{2+} . For example a solution with low
30 $Na:Cl$ ratio raises the phosphorylation potential (See
Table III above). In other circumstances, raising
 $Na:Cl$ outside may raise cellular $[Ca^{2+}]$ for example in
rat liver.

 Having now fully described the invention, it will
35 be apparent to one of ordinary skill in the art that

132

- 1 many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

5

SUBSTITUTE SHEET

1 CLAIMS

1. An in vivo process which (a) tends to maintain the normal plasma milliequivalent ratio of sodium cations to chloride anions in a normal range and (b) tends to
5 maintain normal plasma and cellular pH, and (c) tends to maintain normal cellular cofactor ratios, said process comprising introducing within a living mammal a physiologically effective amount of an aqueous solution comprising
* water which has dissolved therein:

- 10 (A) at least one of the following near equilibrium couples in the respective quantities indicated:
- (1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide
15 wherein the milliequivalent ratio of said bicarbonate anions to said carbon dioxide ranges from about 0.1:1 to 55:0.1,
 - (2) from 0 to about 465 millimoles per liter of a second couple mixture consisting of
20 l-lactate anions and pyruvate anions wherein the milliequivalent ratio of said l-lactate anions to said pyruvate anions ranges from about 20:1 to 1:1,
 - (3) from about 0 to about 465 millimoles per
25 liter of a third couple mixture consisting of d-betahydroxybutyrate to said acetoacetate anions wherein the milliequivalent ratio of said d-betahydroxybutyrate to said acetoacetate ranges from about 6:1 to 0.5:1,
- 30 (B) from about 1 to 2400 millimoles per liter of sodium cations,
- (C) sufficient millimoles per liter of chloride
35 anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range from about 1.24 to 1.6,

134

- 1 (D) optionally from 0 to about 2400 millimoles
per liter of at least one osmotically active
substantially nonionic substance,
- (E) optionally at least one of the following
5 additional cations in a respective quantity
as indicated:

<u>cation</u>	quantity (in millimoles/liter)
potassium	0 - 90
10 calcium	0 - 60
magnesium	0 - 15

the relationship between said water and all
solutes in said water being such that said
solution is characterized by having:

- 15 (1) an osmolarity ranging from about 250
to 5000 milliosmoles;
- (2) a pH in the range from about 5 to 9;
- (3) the charges of all cations equal the
charges of all anions; and
- 20 (4) the minimum total concentration of all
said near equilibrium couples present
in said solution is at least about 0.1
millimole per liter.

2. A physiologically compatible aqueous salt
25 solution for mammalian administration which (a) tends to
maintain a normal plasma milliequivalent ratio of sodium
cations to chloride anions in a normal range, and (b) tends
to maintain normal plasma and cellular pH and tends to
maintain normal cellular co-factor ratios, said solution
30 comprising water which has dissolved therein:

- (A) at least one of the following near equilibrium
couples in the respective quantities indicated:
- (1) from 0 to about 465 millimoles per liter
of a first couple mixture consisting of
35 bicarbonate anions and carbon dioxide
wherein the milliequivalent ratio of said
bicarbonate anions to said carbon dioxide
ranges from about 0.1:1 to 55:0.1,

CONSTITUTE SHEET

135

- 1 (2) from 0 to about 465 millimoles per liter
of a second couple mixture consisting of
1-lactate anions and pyruvate anions
wherein the milliequivalent ratio of said
5 1-lactate anions to said pyruvate anions
ranges from about 20:1 to 1:1,
(3) from about 0 to about 465 millimoles per
liter of a third couple mixture consisting
of d-betahydroxybutyrate anions and
10 acetoacetate anions wherein the milli-
equivalent ratio of said d-betahydroxy-
butyrate to said acetoacetate ranges from
about 6:1 to 0.5:1,
(B) from about 1 to 2400 millimoles per liter of
15 sodium cations,
(C) sufficient millimoles per liter of chloride
anions to produce a milliequivalent ratio of
sodium cations to chloride anions in the range
from about 1.24 to 1.6,
20 (D) optionally from 0 to about 2400 millimoles per
liter of at least one osmotically active
substance,
(E) optionally at least one of the following
additional cations in a respective quantity
25 as indicated:

	<u>cation</u>	quantity (in millimoles/liter)
	potassium	0 - 90
	calcium	0 - 60
30	magnesium	0 - 15

- (F) optionally from 0 to about 25 millimoles per
liter of sigma inorganic phosphate,
(G) optionally from 0 to about 2 millimoles per
liter of sigma inorganic sulfate,
35 the relationship between said water and all solutes in said
water being such that said solution is characterized by
having:

- 1 (1) an osmolarity ranging from about 260
to 5000 milliosmoles;
- (2) a pH in the range from about 5 to 9;
- 5 (3) the charges of all cations equal the
charges of all anions; and
- (4) the minimum total concentration of all
said near equilibrium couples present
in said solution is at least about 0.1
millimoles per liter.
- 10 3. The solution of claim 2 additionally containing
(a) optionally from 0 to about 25 millimoles
per liter of sigma inorganic phosphate,
and
- 15 (b) optionally from 0 to about 2 millimoles
per liter of sigma inorganic sulfate.
4. The solution of claim 2 wherein, of each of
said first, said second, and said third couple mixtures,
a combination of said first couple mixture plus at least
one of either of said second couple mixtures or of said
20 third couple mixture is employed, and whereby both
normalization of cellular co-factor ratios and normali-
zation of both plasma and intracellular fluid pH tends to
be achieved.
5. The solution of claim 2 wherein said nonionic
25 substance is metabolizable and the amount thereof ranges
from 0 to about 15 millimoles per liter of at least one
dissolved metabolizable nonionic osmotically active
substances in said solution is such as to produce a
milliosmolarity therein in the range from about 280 to
30 320.
6. The solution of claim 5 wherein said nonionic
substance comprises glucose.
7. The solution of claim 5 wherein said nonionic
substance is selected from the group consisting of glucose
35 fructose, glycerol, and sorbitol.

1 8. The solution of claim 2 wherein at least one
of said second and said third couple mixtures is employed.

 9. The solution of claim 8 wherein only said
second couple mixture is employed.

5 10. The solution of claim 8 wherein only said
third couple mixture is employed.

 11. The solution of claim 8 wherein said first
couple mixture is additionally present.

 12. The solution of claim 2 wherein each of said
10 first, said second, and said third couple mixtures are
all employed.

 13. The solution of claim 4 wherein said carbon
dioxide is produced in situ by including in said solution
a dissolved mixture of

15 (A) at least one member of the group consisting
of physiologically acceptable bicarbonate
salts, and

 (B) at least one carboxylic acid selected from
the group consisting of l-lactic acid,
20 pyruvic acid, d-betahydroxybutyric acid,
and acetoacetic acid,

and provided that:

(a) the total molar quantity of said carboxylic acid and
the total molar quantity of said bicarbonate salts is such
25 that there is produced in said solution a quantity of
dissolved carbon dioxide sufficient to make said mole
ratio of said bicarbonate anions to said carbon dioxide
fall in within said range, and

(b) the total quantity of all bicarbonate anions remains
30 within a value such that said mole ratio of said bi-
carbonate anions in said solution to said carbon dioxide
falls within said range, and

(c) the total individual quantities of said respective
carboxylic acids is such that said mole ratio of l-lactate
35 to pyruvate, and said mole ratio of d-betahydroxybutyrate
to acetoacetate each remain within said respective ranges.

 14. The solution of claim 2 wherein said mole
ratio of said bicarbonate anions to said carbon dioxide
ranges from about 0.1:1 to 55:0.1.

138

1 15. The solution of claim 2 wherein substantially
the only cation present is sodium.

 16. The solution of claim 2 which contains not
more than two cations one of which is said sodium while
5 the other thereof is selected from the group consisting
of potassium, magnesium, and calcium.

 17. The solution of claim 2 which contains three
cations, one of which is sodium while the others thereof
are selected from the group consisting of potassium,
10 magnesium, and calcium.

 18. The solution of claim 17 wherein said three
cations are sodium, potassium and calcium.

 19. The solution of claim 2 which contains all
four of said cations sodium, potassium, magnesium, and
15 calcium.

 20. An in vivo process for accomplishing elec-
trolyte and fluid therapy which (a) tends to maintain the
normal plasma milliequivalent ratio of sodium cations to
chloride anions in a normal range, and (b) tends to maintain
20 normal plasma and cellular pH, and (c) tends to maintain
normal cellular co-factor ratios, said process comprising
introducing intravenously into a mammal at a physiologically
effective rate an aqueous solution comprising water which
has dissolved therein each of the following components in
25 the respective amounts indicated:

SUBSTITUTE SHEET

1	Component	Quantity Range (millimoles per liter)
	Total cations (mEq/L)	1 to about 2400
	(1) sodium ⁺	1 to about 2400
5	(2) potassium ⁺	0 to about 90
	(3) calcium ⁺⁺	0 to about 60
	(4) magnesium ⁺⁺	0 to about 15
	Total anions (mEq/L)	1 to about 2400
	(5) chloride ⁻	0.6 to about 1940
10	(6) bicarbonate ⁻	0 to about 465
	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 465
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 465
	(9) sum (6, 7, and 8)	0.4 to about 465
15	Total nonionics	0 to about 2400
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 2400
	the relationship between said water and said components being such that the following always holds:	
20	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
25	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmoles/L ranges from about 260 to 5000; and	
	(17) the solution pH ranges from about 5 to 9.	
30	21. A physiologically compatible aqueous salt solution for mammalian administration to accomplish electrolyte and fluid therapy, which (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions, (b) tends to maintain normal plasma and cellular pH, and (c) tends to maintain normal cellular co-factor ratios, said solution comprising water which has dissolved therein each of, the following components in the respective amounts indicated:	

1	Component	Quantity Range (millimoles per liter)
	Total Cations (mEq/L)	1 to about 2400
	(1) sodium ⁺	1 to about 2400
5	(2) potassium ⁺	0 to about 90
	(3) calcium ⁺⁺	0 to about 60
	(4) magnesium ⁺⁺	0 to about 15
	Total Anions (mEq/L)	1 to about 2400
	(5) chloride ⁻	0.6 to about 1940
10	(6) bicarbonate ⁻	0 to about 465
	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 465
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 465
	(9) sum (6, 7 and 8)	0.4 to about 465
15	Total nonionics	0 to about 2400
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 2400
	the relationship between said water and said components being such that the following always holds:	
20	(12) the milliequivalent ratio of HCO ₃ ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
25	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmolarity ranges from about 260 to 5000; and	
30	(17) the solution pH ranges from about 5 to 9.	

22. An in vivo process which (a) tends to maintain the normal plasma milliequivalent ratio of sodium cation to chloride anions in a normal range, and (b) tends to maintain normal cellular co-factor ratios and/or tends to normalize plasma pH, and (c) accomplishes electrolyte and fluid and resuscitation therapy said process comprising intravascularly introducing into blood of a mammal a physiologically effective amount but not more than about

141

- 1 1 liter per 70 kilogram of mammal body weight per day an aqueous solution comprising water which has dissolved therein each of the following components in the respective quantities indicated:

5	Component	Quantity Range
	(millimoles per liter)	
	Total cations (mEq/L)	1 to about 170
	(1) sodium ⁺	1 to about 170
	(2) potassium ⁺	0 to about 10
10	(3) calcium ⁺⁺	0 to about 5
	(4) magnesium ⁺⁺	0 to about 5
	Total anions (mEq/L)	1 to about 170
	(5) chloride ⁻	0.6 to about 137
	(6) bicarbonate ⁻	0 to about 64
15	(7) l-lactate ⁻ + pyruvate ⁻	0 to about 64
	(8) d-betahydroxybutyrate ⁻ + acetoacetate ⁻	0 to about 64
	(9) sum (6, 7 and 8)	0.4 to about 64
	Total nonionics	0 to about 625
20	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 600
	the relationship between said water and said components being such that the following relationships always hold:	
25	(12) the milliequivalent ratio of HCO ₃ ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
30	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmoles/L ranges from about 240 to 950; and	
	(17) the solution pH ranges from about 5 to 9.	

35

- 1 23. A physiologically compatible aqueous salt
 solution for mammalian administration to accomplish
 electrolyte, fluid and resuscitation therapy which (a)
 tends to maintain the normal plasma milliequivalent
 5 ratio of sodium cations to chloride anions in a normal
 range (b) tends to maintain normal plasma and cellular
 pH, and (c) tends to maintain normal cellular co-factor
 ratios, said solution comprising water which has dissolved
 therein each of the following components in the respective
 10 amounts indicated:

		Quantity Range
Component		(millimoles per liter)
	Total cations (mEq/L)	1 to about 170
	(1) sodium ⁺	1 to about 170
15	(2) potassium ⁺	0 to about 10
	(3) calcium ⁺⁺	0 to about 5
	(4) magnesium ⁺⁺	0 to about 5
	Total anions (mEq/L)	1 to about 170
	(5) chloride ⁻	0.6 to about 137
20	(6) bicarbonate ⁻	0 to about 64
	(7) l-lactate ⁻ + pyruvate ⁻	0 to about 64
	(8) d-betahydroxybutyrate ⁻ + acetoacetate ⁻	0 to about 64
	(9) sum (6, 7 and 8)	0.4 to about 64
25	Total nonionics	0 to about 625
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 600
the relationship between said water and said components being such that the following relationships always hold:		
30	(12) the milliequivalent ratio of HCO ₃ ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / 35 acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmoles/L ranges from about 240 to 950;	
	(17) the solution pH ranges from about 5 to 9.	

- 1 24. A dialysis fluid for mammalian administration
 which (a) tends to maintain a normal plasma milliequivalent
 ratio of sodium cations to chloride anions, (b) tends to
 maintain normal plasma and cellular pH, and (c) tends to
 5 maintain normal cellular co-factor ratios, said fluid
 comprising water which has dissolved therein each of the
 following components in the respective amounts indicated:

	Component	Quantity Range (millimoles per liter)
10	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 155
	(2) potassium ⁺	0 to about 6
	(3) calcium ⁺⁺	0 to about 3
	(4) magnesium ⁺⁺	0 to about 2
15	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 81 to 125
	(6) bicarbonate ⁻	0 to about 60
	(7) l-lactate ⁻ plus pyruvate ⁻	0 to about 60
	(8) d-betahydroxybutyrate ⁻ plus	
20	acetoacetate ⁻	0 to about 60
	(9) sum (6+7+8)	about 25 to 60
	Total nonionics	0 to about 525
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 500
25	the relationship between said water and said components being such that:	
	(12) the milliequivalent ratio of HCO ₃ ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ 30 ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
35	(16) the milliosmolarity ranges from about 260 to 850, and	
	(17) the solution pH ranges from about 5 to 9.	

144

1 25. In a hemodialysis process fo the type where
renal function of a living mammal is replaced at least
in part by dialysis and wherein portions of the blood of
said mammal are continuously passed over one face of a
5 dialysis membrane which the opposed face of said dialysis
membrane is contacted with a dialysis fluid, thereby
to achieve a change in the chemical composition of the
body fluids, and wherein said dialysis fluid contains
dissolved therein the same principal inorganic electro-
10 lytes at respective individual concentration levels to
approximating those found in the plasma or serum of
normal mammals of the same species, the improvement which
comprises using as said dialysis fluid an aqueous solution
which has dissolved therein each of the following com-
15 ponents in the respective amounts indicated:

SUBSTITUTE SHEET

145

1	Component	Quantity range
	(millimoles per liter)	
	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 155
5	(2) potassium ⁺	0 to about 5
	(3) calcium ⁺⁺	0 to about 3
	(4) magnesium ⁺⁺	0 to about 2
	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 84 to 125
10	(6) bicarbonate ⁻	about 0 to 55
	(7) l-lactate ⁻ and pyruvate ⁻	about 0 to 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	about 0 to 55
	(9) sum (6+7+8)	about 25 to 55
15	Total nonionics	0 to about 525
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substance	0 to about 500
	the relationship between said water and said components always being such that:	
20	(12) mEq. ratio of bicarbonate ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
	(13) mEq. ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) mEq. ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
25	(15) mEq. ratio of Na:Cl ranges from about 1.24 to 1.6	
	(16) milliosmoles/L ranges from about 260 to 800;	
	(17) pH of solution ranges from about 5 to 9.	

26. A hemodialysis fluid for mammalian administration which (a) tends to maintain a normal plasma milliequi-
 30 valent ratio of sodium cations to chloride anions and (b) tends to maintain normal plasma and cellular pH and (c) tends to maintain normal cellular co-factor ratios, said fluid comprising water which has dissolved therein each of the following components in the respective amounts
 35 indicated:

146

1	Component	Quantity Range (millimoles per liter)
	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 155
5	(2) potassium ⁺	0 to about 5
	(3) calcium ⁺⁺	0 to about 3
	(4) magnesium ⁺⁺	0 to about 2
	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 84 to 125
10	(6) bicarbonate ⁻	about 0 to 55
	(7) l-lactate ⁻ and pyruvate ⁻	about 0 to 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	about 0 to 55
	(9) sum (6+7+8)	about 25 to 55
15	Total nonionics	0 to about 525
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substance	0 to about 500
20	the relationship between said water and said components always being such that:	
	(12) mEq. ratio of bicarbonate ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
	(13) mEq. ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
25	(14) mEq. ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ range from about 6/1 to 0.5/1;	
	(15) mEq. ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) milliosmoles/L ranges from about 260 to 800;	
	(17) pH of solution ranges from about 5 to 9.	

27. In a process of the type where renal function
 30 of a living mammal is replaced at least in part by
 dialysis and wherein a dialysis fluid is charged into the
 peritoneal cavity of such mammal for a time sufficient
 to achieve a change in the chemical composition of the
 body fluids, and wherein said dialysis fluid contains
 35 dissolved therein the same principal inorganic electro-
 lytes at respective individual concentration levels
 approximately those found in the plasma or serum of
 normal mammals of the same species, the improvement

SUBSTITUTE SHEET

147

- 1 which comprises accomplishing simultaneously with such dialysis (a) the maintenance of a normal plasma milliequivalent ratio of sodium cations to chloride anions, (b) the maintenance of normal plasma and cellular pH, and (c) tends to maintain normal cellular co-factor ratios, such improvement being achieved by employing as said dialysis fluid an aqueous solution which has dissolved therein each of the following components in the respective amounts indicated:

10	Component	Quantity Range (millimoles per liter)
	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 165
	(2) potassium ⁺	0 to about 5
15	(3) calcium ⁺⁺	0 to about 2
	(4) magnesium ⁺⁺	0 to about 1.5
	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 81 to 130
	(6) bicarbonate ⁻	0 to about 55
20	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 55
	(9) sum (6+7+8)	about 26 to 55
	Total nonionics	about 40 to 252
25	(10) carbon dioxide	about 0 to 25
	(11) osmotically active substance	about 40 to 250
the relationship between said water and said components always being such that:		
30	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$	ranges from about 0.1/1 to 160/1;
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻	ranges from about 20/1 to 1/1;
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻	ranges from about 6/1 to 0.5/1;
35	(15) the milliequivalent ratio of Na:Cl	ranges from about 1.24 to 1.6;
	(16) the milliosmolarity per liter	ranges from about 311 to 615 and

- 1 (17) the solution pH ranges from about 5 to 8.

28. A peritoneal dialysis fluid for mammalian administration which (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride
 5 anions, (b) tends to maintain normal plasma and cellular pH, and (c) tends to maintain normal cellular co-factor ratios, said fluid comprising water which has dissolved therein each of the following components in the respective amounts indicated:

10	Component	Quantity Range (millimoles per liter)
	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 165
	(2) potassium ⁺	0 to about 5
15	(3) calcium ⁺⁺	0 to about 2
	(4) magnesium ⁺⁺	0 to about 1.5
	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 81 to 130
	(6) bicarbonate ⁻	0 to about 55
20	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 55
	(9) sum (6+7+8)	about 26 to 55
	Total nonionics	about 40 to 252
25	(10) carbon dioxide	about 0 to 25
	(11) osmotically active substance	about 40 to 250

the relationship between said water and said components always being such that:

- (12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from
 30 about 0.1/1 to 160/1;
 (13) the milliequivalent ratio of l-lactate⁻/pyruvate⁻ ranges from about 20/1 to 1/1;
 (14) the milliequivalent ratio of d-betahydroxybutyrate⁻/acetoacetate⁻ ranges from about 6/1 to 0.5/1;
 35 (15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;
 (16) the milliosmolarity per liter ranges from about 311 to 615, and

1 (17) the solution pH ranges from about 5 to 8.

29. A process for regulating:

- 5 (1) distribution of water between intra-cellular and extracellular fluid,
- (2) distribution of the inorganic electrolytes Na, K, Cl, Ca between intracellular and extracellular fluid,
- (3) transmembrane cellular potential,
- comprising contacting a living animal cell with an aqueous
- 10 solution comprising water which has dissolved therein:

(A) at least one of the following near equilibrium couples in the respective quantities indicated:

- (1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide wherein the milliequivalent ratio of said bicarbonate anions to said carbon dioxide anions ranges from 0.1:1 to 55:0.1,
- 15
- (2) from 0 to about 465 millimoles per liter of a second couple mixture consisting of l-lactate anions and pyruvate anions wherein the milliequivalent ratio of said l-lactate anions to said pyruvate anions ranges from about 20:1 to 1:1;
- 20
- (3) from about 0 to about 465 millimoles per liter of a third couple mixture consisting of d-betahydroxybutyrate anions and acetoacetate anions wherein the milliequivalent ratio of said d-betahydroxybutyrate to said acetoacetate ranges from about 6:1 to 0.5:1,
- 25
- (B) from about 1 to 2400 millimoles per liter of sodium cations,
- 30
- (C) sufficient millimoles per liter of chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range from 1.24 to 1.6,
- 35

150

- 1 (D) optionally from 0 to about 2400 millimoles
per liter of at least one osmotically active
substantially nonionic substance,
(E) the following additional cations in the
5 respective quantities indicated:

Cation	Quantity (in millimoles/liter)
potassium	0 - 90
calcium	0 - 60
10 magnesium	0 - 15

the relationship between said water and all solutes in
said water being such that said solution is characterized
by having:

- (1) an osmolarity ranging from about 260 to
15 to 5000 milliosmoles/liter;
(2) a pH in the range from about 5 to 9;
(3) the charges of all cations equal the
charges of all anions, and
(4) the minimum total concentration of all
20 said near equilibrium couples(s) present
in said solution is at least about 0.1
millimole per liter.

30. A process for effecting in a living cell
simultaneously each of:

- 25 (A) the redox state, $[NAD^+]/[NADH]$ or
 $[NADP^+]/[NADPH]$;
(B) the phosphorylation potential,
 $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$
(C) the distribution of H_2O between extra-
30 cellular and intracellular space
(D) the E, (transmembrane potential) and
(E) the T S (an energy term)

by contracting such cell with an aqueous solution
comprising water which has dissolved therein:

35

SUBSTITUTE SHEET

151

- 1 (A) at least one of the following near equilibrium couples in the respective quantities indicated:
- 5 (1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide wherein the milliequivalent ratio of said bicarbonate anions to said carbon dioxide ranges from about 0.1:1 to 55:0.1,
- 10 (2) from 0 to about 465 millimoles per liter of a second couple mixture consisting of l-lactate anions and pyruvate anions wherein the milliequivalent ratio of said l-lactate anions to pyruvate anions ranges from about 20:1 to 1:1,
- 15 (3) from 0 to about 465 millimoles per liter of a third couple consisting of d-betahydroxybutyrate anions and acetoacetate anions wherein the milliequivalent ratio of said d-betahydroxybutyrate to said acetoacetate ranges from about 6:1 to 0.5:1,
- 20 (B) from about 1 to 2400 millimoles per liter of sodium cations;
- 25 (C) sufficient millimoles per liter of chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range from about 1.24 to 1.6.
- 30 (D) optionally from 0 to about 2400 millimoles per liter of at least one osmotically active substance,
- 35 (E) the following additional cations in the respective quantities indicated:

SUBSTITUTE SHEET

152

1	Cations	Quantity (in millimoles/liter)
	potassium	0 - 90
	calcium	0 - 60
5	magnesium	0 - 15

the relationship between said water and all solutes in
said water being such that said solution is characterized
by having: .

- (1) an osmolarity ranging from about 260 to
10 5000 milliosmoles per liter;
- (2) a pH in the range from about 5 to 9;
- (3) the charges of all cations equal the
charges of all anions, and
- (4) the minimum total concentration of all
15 said near equilibrium couples present in
said solution is at least about 0.1
millimole per liter.

20

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US85/01202

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ¹² According to International Patent Classification (IPC) or to both National Classification and IPC INT CL ⁴ A61K 31/56, 31/65, 31/66 and 31/70														
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched ⁴</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%;">Classification System</th> <th style="width: 80%;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; vertical-align: top;">US</td> <td style="text-align: center; vertical-align: top;">424-146, 153 + 180 514-23</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵</div>			Classification System	Classification Symbols	US	424-146, 153 + 180 514-23								
Classification System	Classification Symbols													
US	424-146, 153 + 180 514-23													
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%;">Category [*]</th> <th style="width: 70%;">Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷</th> <th style="width: 20%;">Relevant to Claim No. ¹⁸</th> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">U.S. 3,970,750, Pub. 20 July 1976 Brockemeyer et al</td> <td style="text-align: center; vertical-align: top;">ALL</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">U.S. 3,993,750, Pub. 23 Nov 1976 Fox, Jr. et al</td> <td style="text-align: center; vertical-align: top;">ALL</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">Physicians' Desk Reference, 28th Ed. (1974), p. 1257</td> <td style="text-align: center; vertical-align: top;">ALL</td> </tr> </table>			Category [*]	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸	X	U.S. 3,970,750, Pub. 20 July 1976 Brockemeyer et al	ALL	X	U.S. 3,993,750, Pub. 23 Nov 1976 Fox, Jr. et al	ALL	X	Physicians' Desk Reference, 28th Ed. (1974), p. 1257	ALL
Category [*]	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸												
X	U.S. 3,970,750, Pub. 20 July 1976 Brockemeyer et al	ALL												
X	U.S. 3,993,750, Pub. 23 Nov 1976 Fox, Jr. et al	ALL												
X	Physicians' Desk Reference, 28th Ed. (1974), p. 1257	ALL												
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search ² <div style="text-align: center; font-size: 1.2em;">09 Sept. 1985</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report ² <div style="text-align: center; font-size: 1.2em;">04 OCT 1985</div> </td> </tr> <tr> <td style="width: 50%; padding: 5px;"> International Searching Authority ¹ <div style="text-align: center; font-size: 1.2em;">USA/US</div> </td> <td style="width: 50%; padding: 5px;"> Signature of Authorized Officer ²⁰ <div style="text-align: center;"> Stanley J. Friedman </div> </td> </tr> </table>			Date of the Actual Completion of the International Search ² <div style="text-align: center; font-size: 1.2em;">09 Sept. 1985</div>	Date of Mailing of this International Search Report ² <div style="text-align: center; font-size: 1.2em;">04 OCT 1985</div>	International Searching Authority ¹ <div style="text-align: center; font-size: 1.2em;">USA/US</div>	Signature of Authorized Officer ²⁰ <div style="text-align: center;"> Stanley J. Friedman </div>								
Date of the Actual Completion of the International Search ² <div style="text-align: center; font-size: 1.2em;">09 Sept. 1985</div>	Date of Mailing of this International Search Report ² <div style="text-align: center; font-size: 1.2em;">04 OCT 1985</div>													
International Searching Authority ¹ <div style="text-align: center; font-size: 1.2em;">USA/US</div>	Signature of Authorized Officer ²⁰ <div style="text-align: center;"> Stanley J. Friedman </div>													